Outcomes with Tacrolimus-Based Immunosuppression After Kidney Transplantation from Standard- and Extended-Criteria Donors – A *Post Hoc* Analysis of the Prospective OSAKA Study

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# OSAKA (Optimising immunoSuppression After Kidney transplantation with ADVAGRAF™)
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Background: This *post hoc* analysis of data from the prospective OSAKA study evaluated the efficacy and safety of prolonged- and immediate-release tacrolimus in patients who received kidneys from extended-criteria (ECD) and standard-criteria (SCD) donors.

Material/Methods: Within the ECD and SCD groups, patients were randomized to one of 4 tacrolimus-based regimens (initial dose): Arm 1, immediate-release tacrolimus (0.2 mg/kg/day); Arm 2, prolonged-release tacrolimus (0.2 mg/kg/day); Arm 3, prolonged-release tacrolimus (0.3 mg/kg/day); Arm 4, prolonged-release tacrolimus (0.2 mg/kg/day) plus basiliximab. All patients received mycophenolate mofetil and bolus corticosteroids; Arms 1–3 also received tapered corticosteroids. ECDs met the definition: living/deceased donors aged ≥60 years, or 50–60 years with ≥1 other risk factor, and donation after circulatory death. Primary composite endpoint: graft loss, biopsy-confirmed acute rejection or renal dysfunction by Day 168. Outcomes were compared across treatment arms with the chi-squared or Fisher's exact test.

Results: A total of 1198 patients were included in the analysis (ECD: n=620 [51.8%], SCD: n=578 [48.2%]). Patients with kidneys from ECDs were older versus SCDs (mean age, 55.7 *vs.* 44.5 years, p<0.0001). A higher proportion of patients with kidneys from ECDs versus SCDs met the primary composite endpoint (56.8% *vs.* 32.4%, p<0.0001). However, no statistically significant differences in clinical outcomes or the incidence of treatment-emergent adverse events were seen between treatment arms within each donor group.

Conclusions: Worse outcomes were experienced in patients who received kidneys from ECDs versus SCDs. Prolonged-release tacrolimus provided similar graft survival to the immediate-release formulation, with a manageable tolerability profile.

MeSH Keywords: Immunosuppression • Kidney Transplantation • Tacrolimus

Clinical trial link: https://clinicaltrials.gov/ct2/show/NCT00717470?term=pmr-ec-1210&draw=2&rank=1

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/920041

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Background

The goals of immunosuppression in kidney transplantation are to minimize graft decline and delay graft loss. Recent advances in immunosuppression have significantly enhanced short-term outcomes; over 90% of kidney transplant recipients have graft survival at Year 1 after transplant [1,2]. Despite this, graft loss occurs in approximately half of all patients by Year 10 [2]. The transplant community is, therefore, tasked with developing strategies that will improve long-term graft survival, while attempting to meet the disparity between the limited supply and the rising demand for kidneys available for transplantation.

Over the past decade, extended-criteria donors (ECDs) have been used increasingly as a means of expanding the pool of available kidney donors. Although the use of ECDs has markedly improved recipient survival versus long-term dialysis, it has been associated with poorer long-term outcomes when compared with standard-criteria donors (SCDs) [3–6]. Early differences in immunosuppressive treatment have been shown to affect long-term outcomes [7,8]. With this in mind, there is an ongoing need for the optimization of immunosuppressive regimens and the individualization of therapy to match specific patient situations in order to improve outcomes.

OSAKA (Optimising immunoSuppression After Kidney transplantation with Advagraf™) was a randomized, Phase IIIb trial, over 168 days, which assessed immunosuppressive regimens with immediate-release tacrolimus taken twice daily or prolonged-release tacrolimus taken once daily in *de novo* kidney transplantation. The study showed that the efficacy of prolonged-release tacrolimus 0.2 mg/kg without induction therapy was non-inferior to an immunosuppressive regimen based on the same starting dose of immediate-release tacrolimus without induction therapy [9].

The OSAKA study was conducted in a large number of kidney transplant recipients who were considered to be representative of the European transplant population, in that over 50% of patients received a kidney from an ECD [9]. This *post hoc* analysis of data from the OSAKA study compared the efficacy and safety of 3 prolonged-release and 1 immediate-release tacrolimus-based immunosuppressive regimens in kidney transplant recipients from ECDs and SCDs.

Material and Methods

Study design

OSAKA was a randomized, open-label, parallel-group, Phase IIIb study over 168 days in adults with end-stage renal disease undergoing primary kidney transplantation or retransplantation with ECD or SCD kidneys. An independent ethics committee from each study center granted approval before initiation. Written informed consent was obtained from all participants. The immunosuppressive regimens administered to patients used immediate-release tacrolimus, taken twice daily (Prograf™, Astellas Pharma Ltd, Chertsey, UK, hereafter referred to as immediate-release tacrolimus) or prolonged-release tacrolimus taken once daily (Advagraf™, Astellas Pharma Europe BV, Netherlands, hereafter referred to as prolonged-release tacrolimus). The study design and procedures for OSAKA were reported previously [9]. In brief, patients were randomized 1: 1: 1: 1 to 4 treatment arms:

- Arm 1: immediate-release tacrolimus twice daily (initial dose 0.2 mg/kg/day) plus mycophenolate mofetil (MMF), bolus corticosteroids on Days 0 and 1, and tapered corticosteroids.
- Arm 2: prolonged-release tacrolimus once daily (initial dose 0.2 mg/kg/day) plus MMF, bolus corticosteroids on Days 0 and 1, and tapered corticosteroids.
- Arm 3: prolonged-release tacrolimus once daily (initial dose 0.3 mg/kg/day) plus MMF, bolus corticosteroids on Days 0 and 1, and tapered corticosteroids.
- Arm 4: prolonged-release tacrolimus once daily (initial dose 0.2 mg/kg/day) plus MMF and basiliximab and bolus corticosteroids on Day 0.

Oral doses of immediate-release tacrolimus or prolonged-release tacrolimus were adjusted based on clinical evidence of efficacy and safety after Day 1, taking into account recommended whole blood trough concentrations. MMF was given at a dose of 1 g pre-operatively then 1 g twice daily for 14 days and 0.5 g twice daily thereafter.

Unlike common categorization strategies that classify all living donors as SCDs, in this study ECDs were defined retrospectively as living or deceased donors who were aged 60 years or older, or 50 to 60 years old with one or more other risk factor (cerebrovascular accident as reason for death, hypertension, serum creatinine >1.5 mg/dL) and who donated after circulatory death. All other donors were, by default, considered to be SCDs [9].

Outcomes

The primary endpoint was a composite measure, defined as graft loss, biopsy-confirmed acute rejection (BCAR), or renal dysfunction during the first 168 days after transplantation. Graft loss was defined as retransplantation, nephrectomy, death or dialysis ongoing at study end or at time of premature study discontinuation, unless superseded by follow-up information that indicated graft survival. Renal dysfunction was defined as estimated glomerular filtration rate (eGFR) <40 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease-4 (MDRD4) formula. Transplant recipients who never
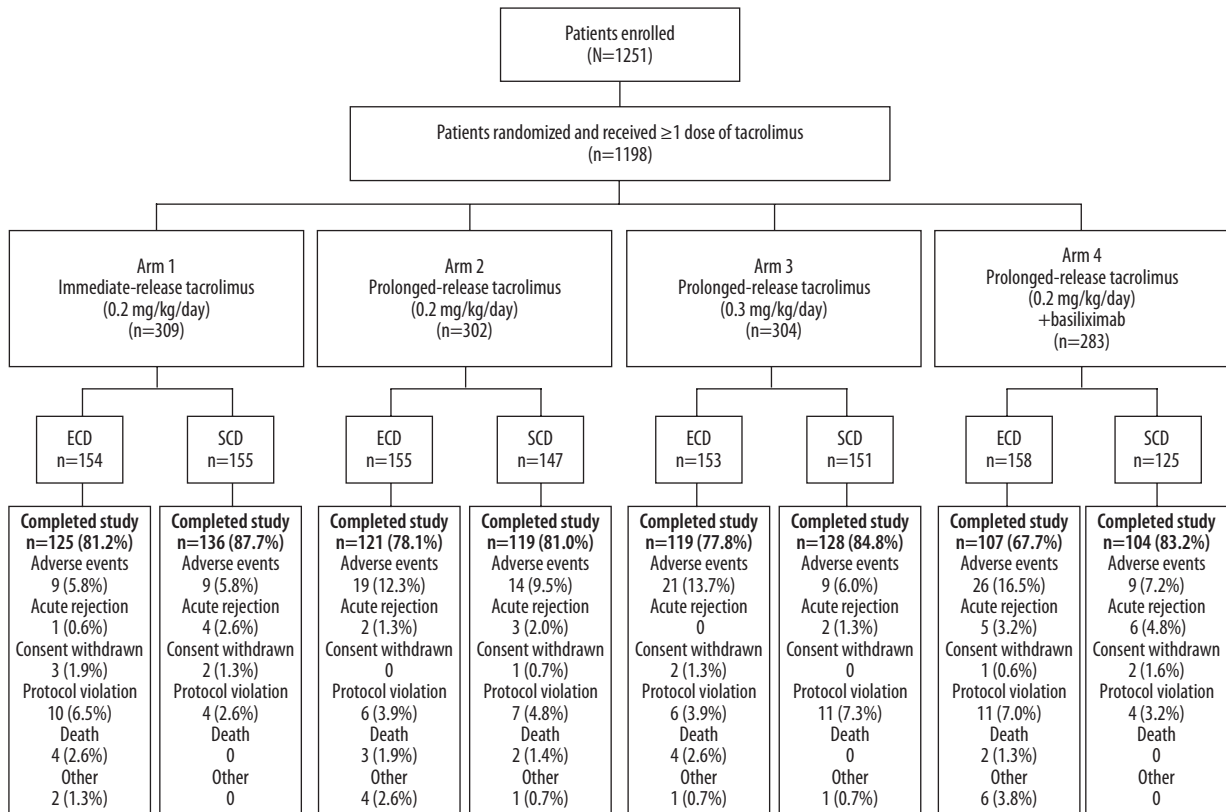
Figure 1. Flow of patients throughout the study, stratified by ECDs and SCDs (FAS). A total of 1198 patients were randomized and received ≥1 dose of tacrolimus; FAS according to treatment group and donor criteria is shown. ECD – extended-criteria donor; FAS – full-analysis set; SCD – standard-criteria donor.

achieved an eGFR >40 mL/min/1.73 m² were classified as having early renal dysfunction, defined as renal dysfunction by Day 2 after transplant. Incidence of BCAR (based on local pathology, based on Banff 97 criteria) during the first 168 days after transplant and delayed graft function (DGF) (defined as dialysis for more than 1 day within the first week after transplant) were also evaluated. Adverse events (AEs) were monitored throughout the study. Post-transplantation diabetes mellitus (PTDM; termed new-onset diabetes mellitus in the original OSAKA study) was defined as fasting blood glucose levels of ≥7 mmol/L from Day 2 onwards. Ongoing diabetes requiring therapy and toxic nephropathy were both reported as AEs by the study investigators.

Statistical analyses

The primary analysis of the composite endpoint for the OSAKA study was undertaken on the per-protocol set, defined as randomized patients who received ≥1 dose of study medication, who had undergone transplantation and who did not have a major protocol violation [9]. This *post hoc* analysis of efficacy and tolerability across the 4 treatment arms in each donor group (ECD and SCD) was undertaken using the full-analysis set (FAS), which comprised all randomized patients who received ≥1 dose of tacrolimus and who had undergone transplantation. Comparisons of categorical variables were evaluated using Fisher's exact test (for 2×2 contingency tables) and a chi-squared test (for 2×4 contingency tables), and continuous variables were evaluated using a *t*-test. All comparisons were at the 0.05 level of significance with no adjustments for multiplicity.

Results

Donor and patient demographics

A total of 1251 patients were enrolled in the OSAKA study; of the 1198 patients included in the FAS, 620 (51.8%) received kidneys from ECDs and 578 (48.2%) from SCDs. The number of patients receiving kidneys from ECDs was similar across treatment arms (Figure 1). For the whole population, baseline characteristics were comparable between donor groups [9]; however, as expected, mean (SD) donor age was significantly

Table 1. Baseline characteristics stratified by treatment arm and donor group (FAS).

Characteristic, n (%)	Arm 1 Immediate-release tacrolimus 0.2 mg/kg/day		Arm 2 Prolonged-release tacrolimus 0.2 mg/kg/day		Arm 3 Prolonged-release tacrolimus 0.3 mg/kg/day		Arm 4 Prolonged-release tacrolimus 0.2 mg/kg/day +basiliximab	
	ECD n=154	SCD n=155	ECD n=155	SCD n=147	ECD n=153	SCD n=151	ECD n=158	SCD n=125
Transplant recipients								
Sex								
Male	110 (71.4)	101 (65.2)	106 (68.4)	100 (68.0)	104 (68.0)	100 (66.2)	109 (69.0)	76 (60.8)
Female	44 (28.6)	54 (34.8)	49 (31.6)	47 (32.0)	49 (32.0)	51 (33.8)	49 (31.0)	49 (39.2)
Mean (SD) age, years	56.5 (11.4)*	45.2 (12.8)*	56.3 (11.3)*	44.7 (12.0)*	55.6 (11.9)*	44.7 (13.2)*	54.4 (12.3)*	42.8 (12.1)*
Race								
Caucasian	150 (97.4)	146 (94.2)	147 (94.8)	137 (93.2)	148 (96.7)	143 (94.7)	151 (95.6)	114 (91.2)
Black	2 (1.3)	4 (2.6)	6 (3.9)	8 (5.4)	4 (2.6)	3 (2.0)	5 (3.2)	6 (4.8)
Asian/other	2 (1.3)	5 (3.2)	2 (1.3)	2 (1.4)	1 (0.7)	5 (3.3)	2 (1.3)	5 (4.0)
Mean (SD) BMI	25.3 (4.3)	25.5 (4.2)	25.7 (4.1)	25.9 (4.7)	26.2 (4.3)†	24.8 (4.5)†	25.3 (3.7)	25.2 (4.2)
Transplant								
First transplant	147 (95.5)	149 (96.1)	147 (94.8)	141 (95.9)	146 (95.4)	140 (92.7)	150 (94.9)	117 (93.6)
Retransplant	7 (4.5)	6 (3.9)	8 (5.2)	6 (4.1)	7 (4.6)	11 (7.3)	8 (5.1)	8 (6.4)
Original renal disease								
Diabetic nephropathy	20 (13.0)‡	4 (2.6)‡	20 (12.9)§	8 (5.4)§	14 (9.2)	8 (5.3)	11 (7.0)	10 (8.0)
Focal segmental glomerulosclerosis	3 (1.9)	4 (2.6)	8 (5.2)	6 (4.1)	5 (3.3)	2 (1.3)	2 (1.3)	6 (4.8)
Glomerulonephritis	26 (16.9)	24 (15.5)	20 (12.9)	20 (13.6)	26 (17.0)	35 (23.2)	29 (18.4)	19 (15.2)
Nephrosclerosis	22 (14.3)	18 (11.6)	13 (8.4)	11 (7.5)	21 (13.7)	13 (8.6)	16 (10.1)	10 (8.0)
IgA-nephropathy	8 (5.2)	17 (11.0)	18 (11.6)	13 (8.8)	7 (4.6)	14 (9.3)	14 (8.9)	10 (8.0)
Obstructive uropathy	2 (1.3)	9 (5.8)	6 (3.9)	13 (8.8)	4 (2.6)	10 (6.6)	8 (5.1)	11 (8.8)
Polycystic disease	34 (22.1)	26 (16.8)	27 (17.4)	16 (10.9)	30 (19.6)	22 (14.6)	29 (18.4)	20 (16.0)
Other	25 (16.2)	40 (25.8)	21 (13.5)	41 (27.9)	25 (16.3)	33 (21.9)	36 (22.8)	32 (25.6)
Unknown	14 (9.1)	13 (8.4)	22 (14.2)	19 (12.9)	21 (13.7)	14 (9.3)	13 (8.2)	7 (5.6)
Donors								
Sex								
Male	82 (53.2)	96 (61.9)	83 (53.5)	76 (51.7)	70 (45.8)@	93 (61.6)@	87 (55.1)	70 (56.0)
Female	72 (46.8)	58 (37.4)	72 (46.5)	71 (48.3)	83 (54.2)@	58 (38.4)@	71 (44.9)	55 (44.0)
Mean (SD) age, years	61.6 (9.4)*	41.3 (11.7)*	62.1 (8.7)*	41.1 (11.5)*	61.8 (8.3)*	38.8 (11.6)*	61.1 (8.6)*	40.9 (11.5)*
Mean (SD) total HLA mismatches	3.4 (1.3)¶	2.9 (1.4)¶	3.3 (1.3)**	2.9 (1.4)**	3.3 (1.5)	3.1 (1.4)	3.1 (1.3)	2.8 (1.5)
Mean (SD) CIT, hours††	14.3 (5.5)	15.9 (5.7)	15.4 (5.8)	14.7 (5.7)	15.1 (5.6)	15.8 (6.2)	15.5 (5.8)	15.6 (5.9)
CMV D+, R–	25 (16.2)	26 (16.8)	21 (13.5)	19 (12.9)	32 (20.9)	22 (14.6)	34 (21.5)	22 (17.6)
Mean (SD) serum creatinine, mg/dL	0.95 (0.39)	0.98 (0.43)	0.97 (0.49)	0.98 (0.56)	0.95 (0.45)	0.98 (0.51)	1.02 (0.54)	1.10 (0.89)
Type of donor								
Living	11 (7.1)	30 (19.4)	5 (3.2)	29 (19.7)	7 (4.6)	26 (17.2)	9 (5.7)	27 (21.6)
Deceased	143 (92.9)	125 (80.6)	150 (96.8)	118 (80.3)	146 (95.4)	125 (82.8)	149 (94.3)	98 (78.4)

P values denote significance for ECD *vs.* SCD groups within treatment arms; * p<0.0001; † p=0.0059; ‡ p=0.0006; § p=0.0292; @ p=0.006; ¶ p=0.0032; ** p=0.0143; all other p values were non-significant; †† deceased donors only; all values are n (%), unless otherwise specified. BMI – body mass index; CIT – cold ischemia time; CMV – cytomegalovirus; D – donor; ECD – extended-criteria donors; FAS – full-analysis set; HLA – human leukocyte antigen; IgA – immunoglobulin A; R – recipient; SCD – standard-criteria donors; SD – standard deviation.

Table 2. Mean tacrolimus trough levels (ng/mL) throughout the 168-day study period, stratified by treatment arm and donor group (FAS).

Day	Arm 1 Immediate-release tacrolimus 0.2 mg/kg/day			Arm 2 Prolonged-release tacrolimus 0.2 mg/kg/day			Arm 3 Prolonged-release tacrolimus 0.3 mg/kg/day			Arm 4 Prolonged-release tacrolimus 0.2 mg/kg/day+basiliximab		
	ECD n=154	SCD n=155	P value	ECD n=155	SCD n=147	P value	ECD n=153	SCD n=151	P value	ECD n=158	SCD n=125	P value
1	16.4 (8.9)	15.6 (8.6)	0.4980	13.3 (9.0)	12.5 (9.4)	0.4884	18.3 (10.3)	16.6 (10.9)	0.1947	12.5 (7.3)	11.1 (5.8)	0.1405
7	12.0 (5.8)	11.7 (4.2)	0.5483	12.0 (6.5)	11.8 (6.0)	0.7357	13.8 (7.1)	13.1 (9.7)	0.5223	12.8 (6.1)	12.0 (6.8)	0.3176
14	10.5 (3.9)	11.9 (3.9)	0.0024	10.8 (4.4)	11.0 (4.6)	0.6600	10.9 (4.1)	11.0 (4.2)	0.7396	11.4 (4.9)	11.8 (5.0)	0.5155
28	10.8 (4.4)	11.8 (4.2)	0.0412	11.3 (4.3)	12.2 (5.6)	0.1326	11.5 (4.0)	12.7 (4.5)	0.0198	12.2 (5.4)	12.0 (4.8)	0.7360
84	9.6 (3.4)	9.7 (3.8)	0.9381	9.3 (3.5)	9.7 (2.8)	0.2842	9.5 (3.0)	9.9 (3.6)	0.3491	10.3 (4.8)	10.2 (4.6)	0.8741
168	8.2 (3.0)	8.4 (3.1)	0.5935	8.7 (3.6)	8.7 (2.6)	0.9742	8.8 (4.4)	8.9 (3.3)	0.7806	8.0 (2.3)	8.2 (2.5)	0.4858

All values are mean (SD), unless otherwise specified; p values were calculated using a t-test. ECD – extended-criteria donors; FAS – full-analysis set; SCD – standard-criteria donors; SD – standard deviation.

higher among ECDs versus SCDs (61.6 [8.8] *vs.* 40.5 [11.6] years, p<0.0001). Mean (SD) patient age was also significantly higher among those receiving kidneys from ECDs versus SCDs (55.7 [11.7] *vs.* 44.5 [12.6] years, p<0.0001). Comparing treatment arms by donor group, significantly more patients with organs from ECDs in Arms 1 and 2 had diabetic nephropathy compared with those with organs from SCDs (Table 1; p=0.0006 and p=0.0292, respectively). The mean total number of human-leukocyte antigen (HLA) mismatches was higher in the ECD group versus the SCD group for Arms 1 and 2 (p=0.0032 and p=0.0143, respectively).

Tacrolimus dosing

Dose by study arm is shown in Supplementary Table 1.

Consistent with the study design, mean tacrolimus dose at Week 1 was higher in Arm 3 compared with the other arms. Mean prolonged-release tacrolimus doses were generally higher compared with immediate-release tacrolimus at each time point; doses decreased throughout the study for all arms.

Tacrolimus trough levels

A general decline in mean tacrolimus exposure was observed throughout the study in all arms, regardless of whether the kidney was from an ECD or SCD. In the overall ECD versus SCD groups, mean tacrolimus trough levels were clinically comparable (Table 2).

Primary composite endpoint

A total of 539 of the 1198 patients (45.0%) met the criteria for the primary composite endpoint. The overall incidence of patients who met the composite endpoint by Day 168 after transplant was significantly higher in patients with kidneys from ECDs versus SCDs (56.8% [352 of 620] *vs.* 32.4% [187 of 578], p<0.0001). Within each treatment arm, the incidence of patients who met the composite endpoint was significantly higher in the ECD versus SCD groups (p<0.01; Table 3). However, the incidence of patients who met the composite endpoint did not differ significantly across treatment arms among patients with kidneys from ECDs (p=0.7770) or SCDs (p=0.2770) (Figure 2). The incidence of the composite endpoint was similar in patients with kidneys received from deceased donors compared with living donors in the ECD group (56.6% *vs.* 50.0%, respectively) and in the SCD group (32.8% *vs.* 30.4%, respectively) (Supplementary Table 2). However, the number of living donors was low in the ECD group, limiting the robustness of these results.

Renal function

A total of 455 of the 1198 patients (38.0%) met the criteria for renal dysfunction by Day 168. Renal dysfunction was more frequently observed in the overall ECD versus SCD groups (50.8% [315 of 620] *vs.* 24.2% [140 of 578], p<0.0001). The incidence of renal dysfunction in each treatment arm was significantly higher for patients with kidneys from ECDs versus SCDs (p<0.0001 for all comparisons). However, as shown in Figure 3, there were no statistically significant differences in renal dysfunction across treatment arms in either donor group (ECDs: p=0.5011; SCDs: p=0.5418).

Table 3. Incidence of primary composite endpoint, stratified by treatment arm and donor group (FAS).

	Arm 1 Immediate-release tacrolimus 0.2 mg/kg/day		Arm 2 Prolonged-release tacrolimus 0.2 mg/kg/day		Arm 3 Prolonged-release tacrolimus 0.3 mg/kg/day		Arm 4 Prolonged-release tacrolimus 0.2 mg/kg/day +basiliximab		All	
	ECD n=154	SCD n=155	ECD n=155	SCD n=147	ECD n=153	SCD n=151	ECD n=158	SCD n=125	ECD n=620	SCD n=578
Composite endpoint	85 (55.2)	48 (31.0)	85 (54.8)	47 (32.0)	92 (60.1)	43 (28.5)	90 (57.0)	49 (39.2)	352 (56.8)	187 (32.4)
	p<0.0001		p<0.0001		p<0.0001		p=0.004		p<0.0001	
Renal dysfunction	73 (47.4)	38 (24.5)	75 (48.4)	33 (22.4)	80 (52.3)	33 (21.9)	87 (55.1)	36 (28.8)	315 (50.8)	140 (24.2)
	p<0.0001		p<0.0001		p<0.0001		p<0.0001		p<0.0001	
Graft loss	13 (8.4)	5 (3.2)	16 (10.3)	13 (8.8)	15 (9.8)	5 (3.3)	15 (9.5)	8 (6.4)	59 (9.5)	31 (5.4)
	p=0.0556		p=0.6999		p=0.0350		p=0.3878		p=0.0082	
BCAR	24 (15.6)	18 (11.6)	19 (12.3)	12 (8.2)	30 (19.6)	19 (12.6)	21 (13.3)	15 (12.0)	94 (15.2)	64 (11.1)
	p=0.3242		p=0.2608		p=0.1186		p=0.8579		p=0.0403	

Data are n (%), unless otherwise specified; p values were calculated using Fisher's exact test; renal dysfunction was defined as eGFR (MDRD4) <40 mL/min/1.73 m^2. BCAR – biopsy-confirmed acute rejection; ECD – extended-criteria donors; eGFR – estimated glomerular filtration rate; FAS – full-analysis set; MDRD4 – Modification of Diet in Renal Disease-4; SCD – standard-criteria donors.
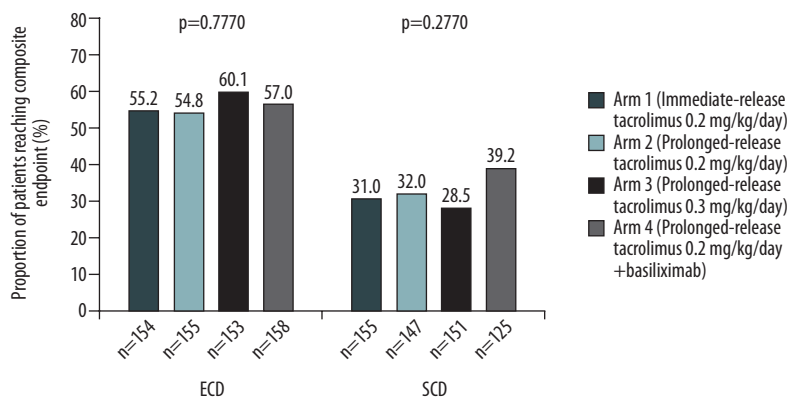

Figure 2. Incidence of composite endpoint by Day 168 in patients who received kidneys from ECDs and SCDs (FAS). The composite endpoint of efficacy failure was defined as graft loss (retransplantation, nephrectomy, death or dialysis ongoing at study end or at time of premature study discontinuation), BCAR diagnosed locally, or renal dysfunction (eGFR [MDRD4] <40 mL/min/1.73 m^2) by Day 168. P values shown are those across all treatment arms for ECDs and SCDs, calculated using the chi-squared test. BCAR – biopsy-confirmed acute rejection; ECD – extended-criteria donor; eGFR – estimated glomerular filtration rate; FAS – full-analysis set; MDRD4 – Modification of Diet in Renal Disease-4; SCD – standard-criteria donor.

Of the 455 patients with renal dysfunction, 27.0% had early renal dysfunction by Day 2. Overall, the incidence of renal dysfunction was significantly higher in the ECD versus SCD groups when only considering patients with renal dysfunction by Day 2 (36.9% [229 of 620] *vs.* 13.3% [77 of 578], p=0.0002) and in patients who experienced renal dysfunction after Day 2 (Day 3 to Day 168) (13.9% [86 of 620] *vs.* 10.9% [63 of 578], p=0.0002).

At Day 168 in the overall group, mean eGFR was significantly lower in recipients of kidneys from ECDs versus SCDs (42.7 *vs.* 54.4 mL/min/1.73 m^2, p<0.0001). The mean eGFR for patients who received kidneys from ECDs was also significantly lower in each treatment arm at Day 168 compared with the eGFR of those who received kidneys from SCDs (Arm 1: 43.5 *vs.* 56.1 mL/min/1.73 m^2; Arm 2: 42.8 *vs.* 55.7 mL/min/1.73 m^2; Arm 3:
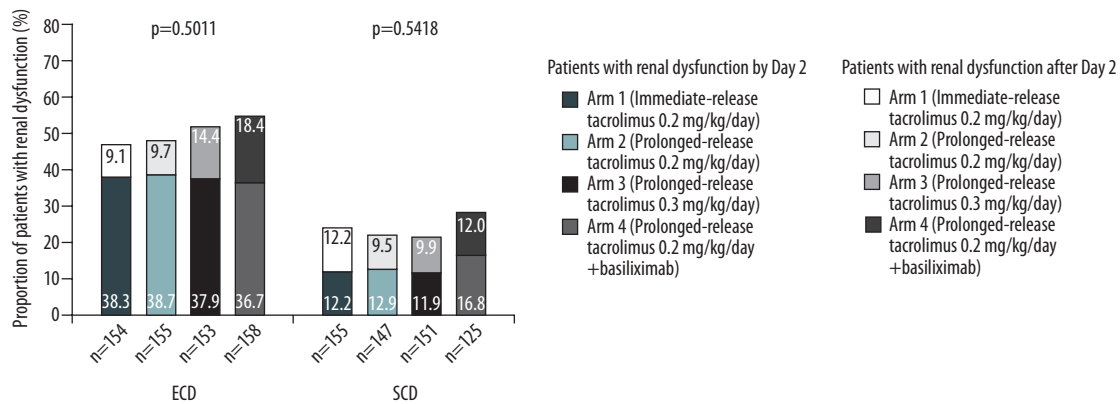
Figure 3. Incidence of renal dysfunction by Day 2 and after Day 2 (Day 3 to Day 168) in patients receiving kidneys from ECDs and SCDs (FAS). Renal dysfunction was defined as eGFR (MDRD4) <40 mL/min/1.73 m^2. P values shown are those across all treatment arms for ECDs and SCDs, calculated using the chi-squared test. ECD – extended-criteria donor; eGFR – estimated glomerular filtration rate; FAS – full-analysis set; MDRD4 – Modification of Diet in Renal Disease-4; SCD – standard-criteria donor.

42.4 *vs.* 54.6 mL/min/1.73 m^2; Arm 4: 42.0 *vs.* 50.2 mL/min/1.73 m^2; for all comparisons p<0.0001).

Graft loss

Overall, graft loss was significantly higher in patients who received kidneys from ECDs versus SCDs (9.5% [59 of 620] *vs.* 5.4% [31 of 578], p=0.0082); for each treatment arm, the numerically higher incidence of graft loss with ECDs versus SCDs reached significance only in Arm 3 (p=0.0350, Table 3). The main causes of graft loss in the overall ECD group were nonfunctioning graft (n=17), technical complications (n=14), and death with functioning graft (n=12); in the SCD group, technical complications (n=16) were the main causes of graft loss, followed by death (n=5) and infection (n=4). There were no statistically significant differences in graft loss across treatment arms in either donor group (ECDs: p=0.9523; SCDs: p=0.0928).

Biopsy-confirmed acute rejection

The incidence of BCAR by Day 168 was low overall, but a higher incidence was reported with ECDs versus SCDs (15.2% [94 of 620] *vs.* 11.1% [64 of 578], p=0.0403). The difference did not reach significance when analyzed for each treatment arm (Table 3). BCAR Banff grade IA–IIA and grade IIB–III were reported for 13.7% (85 of 620) and 1.5% (9 of 620) of patients in the ECD group and 9.9% (57 of 578) and 1.2% (7 of 578) in the SCD group, respectively. There were no statistically significant differences in incidence of BCAR across treatment arms in either donor group (ECDs: p=0.2857; SCDs: p=0.6303; Supplementary Figure 1).

In patients who experienced BCAR, mean tacrolimus trough levels were comparable between the ECD and SCD groups

throughout the 168-day study. There were no statistically significant differences in mean trough levels in patients with and without BCAR on Days 1, 7, 14, 28, 84, and 168 in patients receiving kidneys from SCDs or ECDs.

Tolerability

The rate of treatment-emergent AEs was consistent across treatment arms (94–96%) (Supplementary Table 3), and most (~70% [830 of 1214]) were of mild/moderate severity [9]. Overall, a significantly higher incidence of anemia, diarrhea, DGF, edema, renal impairment, cytomegalovirus (CMV) infections, and toxic nephropathy was observed with ECDs versus SCDs. A total of 85 (13.7%) patients in the ECD group experienced opportunistic infections (82 cases of CMV infection, 2 cases of aspergillus infection and 1 case of pneumocystis) compared with 28 (4.8%) patients in the SCD group (all CMV infections). Toxic nephropathy was reported in 6.6% of the ECD group compared with 3.8% of the SCD group; however, biopsy-proven nephrotoxicity was reported at lower rates (2.9% and 1.7%, respectively). The incidence of DGF was significantly higher in patients who received kidneys from ECDs versus SCDs (p<0.0001); this reached statistical significance in Arms 1 and 4 (for both comparisons: p<0.01; incidence presented in Supplementary Table 3).

The primary OSAKA study reported that the incidence of PTDM after transplantation was comparable between treatment arms [9]. The present analysis showed a nominally significant difference in PTDM incidence between the overall ECD versus SCD groups (17.3% [89 of 513] *vs.* 12.7% [67 of 526], p=0.0455). Overall, ongoing diabetes requiring therapy was comparable between patients with kidneys from ECDs versus SCDs.

Of the patients who completed the study (n=959) or had a functioning graft at follow-up after withdrawal from the study (n=139), only 42 patients (3.8%; 29 patients with ECD and 13 with SCD) were converted to another immunosuppressive therapy (predominantly sirolimus [n=14], ciclosporin [n=11], and everolimus [n=8]), indicating that tacrolimus was well tolerated in this patient population.

Discussion

The shortage of kidneys available for transplant has resulted in a marked increase in the use of organs from ECDs over the past decade. The donor population in Europe is growing older, and non-traumatic donors constitute a majority. Age-matching kidneys between recipient and donor ('old-for-old' transplantation) is a policy of Eurotransplant and is becoming standard practice in many countries [10]. As a result, donor kidney classification also defines different recipient populations. It is, therefore, important that the efficacy and safety of immunosuppressive regimens are evaluated in patients receiving organs from ECDs.

The OSAKA study was conducted in 22 countries, including 19 European countries, and the study population therefore reflects European standards of kidney donation and donor kidney allocation. Clinical trials of immunosuppressive regimens in kidney transplant patients typically include patients who received organs from donors meeting SCD criteria. However, approximately half of the patients in the OSAKA study received a kidney from an ECD, compared with 9% to 33% in other clinical trials [6,9,11,12]. Therefore, OSAKA is well placed to evaluate outcomes in a population more closely resembling the European transplant population compared with other clinical trials.

The primary analysis of OSAKA showed that, in adult *de novo* kidney transplantation, once-daily administration of prolonged-release tacrolimus 0.2 mg/kg without induction therapy was non-inferior to an immunosuppressive regimen based on immediate-release tacrolimus at the same starting dose without induction therapy [9]. Reassuringly, the present *post hoc* analysis showed that prolonged-release tacrolimus also produces comparable outcomes to immediate-release tacrolimus when used in patients receiving kidneys from ECDs. The incidence of the composite endpoint (graft loss, BCAR or renal dysfunction during the first 168 days after transplantation) was comparable with all 4 treatment regimens within the ECD donor group and within the SCD donor group.

Renal dysfunction was the main driver of the composite endpoint in the primary analysis of OSAKA [9] and in the present *post hoc* analysis. Most patients who experienced renal dysfunction did so by Day 2 after transplantation. The incidence

of renal dysfunction by Day 2 and after Day 2 was similar in each treatment arm irrespective of whether the patient was in the ECD or the SCD donor group. Likewise, no significant difference between treatment arms was observed for the incidence of graft loss and BCAR, regardless of donor group. Overall, the results of the *post hoc* analysis indicate that prolonged-release tacrolimus-based immunosuppression is as efficacious as immediate-release tacrolimus in *de novo* kidney transplantation regardless of ECD or SCD group.

It is well established that patients who receive a kidney from an ECD have poorer outcomes than patients who receive a kidney from an SCD [3–6]. Our *post hoc* analysis of OSAKA confirmed previous studies in this regard, with a significantly higher incidence of the composite endpoint and renal dysfunction in patients in the ECD group versus the SCD group. The rates of BCAR and graft loss in this analysis were low, but again, the incidence of BCAR was higher in patients who received organs from ECDs versus SCDs. The incidence of DGF was also significantly higher in patients in the ECD group compared with the SCD group, which reached statistical significance in Arms 1 and 4. DGF is a common complication seen in patients with kidneys from ECDs and has been associated with poor 1-year graft survival [13]. A leading risk factor for DGF is increased cold ischemia time (CIT) [14]; however, in the present study, no significant difference in CIT was observed between the ECD and SCD groups.

The observation that efficacy outcomes were generally worse in patients receiving a kidney from an ECD versus an SCD is not surprising, since kidneys from ECDs are often associated with a higher degree of histologic damage than kidneys from SCDs [15], which may lead to poorer renal function [12,16]. Furthermore, patients in OSAKA who received kidneys from ECDs were older and more likely to have other risk factors for poor outcomes than patients who received kidneys from SCDs, in line with 'old-for-old' kidney transplant policy. Overall, the findings from this *post hoc* analysis indicate that donor criteria had a significant impact on the clinical outcomes of kidney transplant patients receiving a tacrolimus-based immunosuppressive regimen, but treatment regimen within donor group did not.

Mean tacrolimus trough levels were clinically comparable in patients receiving kidneys from ECDs versus SCDs from Day 7 until the end of the study. Tacrolimus trough levels of 5–15 ng/mL were achieved early after prolonged-release tacrolimus initiation in all arms, regardless of the donor origin and the presence or absence of DGF. No new safety signals were observed in this analysis. The safety and tolerability profiles of immediate-release tacrolimus and prolonged-release tacrolimus were similar across all treatment arms in both donor groups. The incidence of several AEs was higher in the ECD group compared

with the SCD group. This is not surprising because many AEs reported in treatment populations (such as anemia and diarrhea) are patient- rather than donor-related, and patients in the ECD group were older and in worse health than those in the SCD group. Importantly, safety findings within each donor group were not markedly different between the treatment arms.

The limitations of the OSAKA study have been reported previously [9]. Further limitations are the relatively short study duration and the lack of kidney donor profile index (KDPI) data, as the KDPI was not introduced until after completion of OSAKA. The different definitions of ECDs and lack of KDPI data hinder comparisons with other trials. The definitions of ECDs and SCDs in this study were determined retrospectively and OSAKA was not designed to provide an in-depth analysis of different donor-recipient couples. Although comparing the efficacy of immunosuppressive regimens in patients receiving kidneys from ECDs across different studies would be interesting, it is problematic because of the varying definitions of ECD used and the different duration of follow-up (Supplementary Table 4). To further reduce the differences between the long-term outcomes of patients who receive organs from ECDs and SCDs, a reduction of HLA-mismatching and CIT in addition to continued optimization of the immunosuppressive regimens remain the most viable options. As such, the results of this study may be particularly applicable to clinical practice.

Conclusions

In this *post hoc* analysis of the OSAKA study, donor criteria influenced the protocol-defined endpoints, with worse outcomes experienced in patients who received kidneys from ECDs versus SCDs. However, within each donor group, the use of prolonged- and immediate-release tacrolimus provided similar graft survival, low incidence rates of BCAR, and a manageable tolerability profile over 168 days of treatment. These data are of increasing importance as the use of organs from ECDs continues to rise in kidney transplantation. Overall, the results from this study indicate that in treatment populations with a high number of kidneys from ECDs, prolonged-release tacrolimus is a viable alternative to immediate-release tacrolimus.

Supplementary Data

Supplementary Table 1. Mean daily tacrolimus dose throughout the 168-day study period, stratified by treatment arm and donor group (FAS).
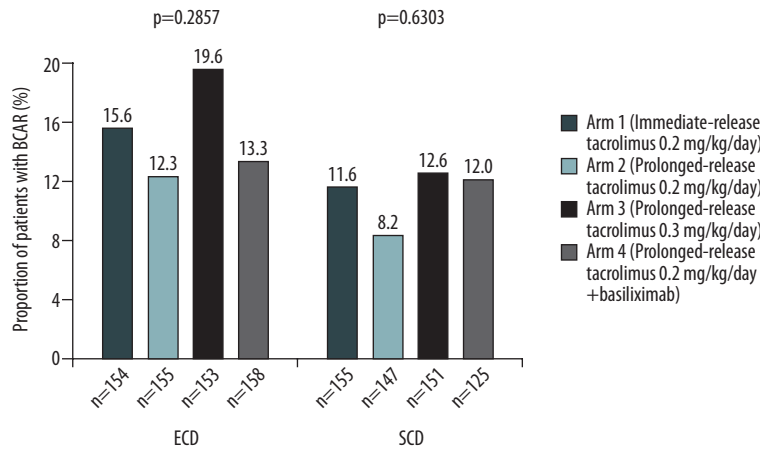
Day	Arm 1 Immediate-release tacrolimus 0.2 mg/kg/day			Arm 2 Prolonged-release tacrolimus 0.2 mg/kg/day			Arm 3 Prolonged-release tacrolimus 0.3 mg/kg/day			Arm 4 Prolonged-release tacrolimus 0.2 mg/kg/day+basiliximab		
	ECD n=154	SCD n=155	P value	ECD n=155	SCD n=147	P value	ECD n=153	SCD n=151	P value	ECD n=158	SCD n=125	P value
1	0.174 (0.046)	0.174 (0.052)	1.000	0.156 (0.051)	0.171 (0.045)	0.014	0.241 (0.072)	0.243 (0.076)	0.828	0.168 (0.046)	0.171 (0.050)	0.634
7	0.144 (0.081)	0.161 (0.064)	0.048	0.146 (0.064)	0.170 (0.068)	0.003	0.169 (0.096)	0.209 (0.094)	0.001	0.151 (0.062)	0.177 (0.068)	0.001
14	0.157 (0.098)	0.172 (0.077)	0.154	0.165 (0.084)	0.199 (0.097)	0.002	0.190 (0.119)	0.224 (0.094)	0.008	0.158 (0.075)	0.192 (0.082)	0.001
28	0.143 (0.104)	0.152 (0.071)	0.401	0.159 (0.090)	0.186 (0.102)	0.023	0.178 (0.115)	0.215 (0.096)	0.004	0.151 (0.076)	0.181 (0.082)	0.004
84	0.110 (0.079)	0.101 (0.059)	0.295	0.112 (0.076)	0.134 (0.092)	0.039	0.122 (0.088)	0.148 (0.085)	0.001	0.108 (0.064)	0.128 (0.071)	0.029
168	0.093 (0.075)	0.086 (0.047)	0.374	0.095 (0.071)	0.111 (0.076)	0.087	0.098 (0.061)	0.118 (0.074)	0.020	0.089 (0.053)	0.105 (0.062)	0.044

All values are mean (SD), unless specified otherwise; p values were calculated using a *t*-test. ECD – extended-criteria donors; FAS – full-analysis set; SCD – standard-criteria donors; SD – standard deviation.

Supplementary Table 2. Incidence of primary composite endpoint, stratified by treatment arm, donor group and donor status (living or deceased) (FAS).

	Arm 1 Immediate-release tacrolimus 0.2 mg/kg/day		Arm 2 Prolonged-release tacrolimus 0.2 mg/kg/day		Arm 3 Prolonged-release tacrolimus 0.3 mg/kg/day		Arm 4 Prolonged-release tacrolimus 0.2 mg/kg/day +basiliximab		All	
	ECD	SCD	ECD	SCD	ECD	SCD	ECD	SCD	ECD	SCD
Deceased donor, N Composite endpoint, n (%)	143 80 (55.9)	125 38 (30.4)	150 82 (54.7)	118 36 (30.5)	146 85 (58.2)	125 37 (29.6)	149 86 (57.7)	98 42 (42.9)	588 333 (56.6)	466 153 (32.8)
Living donor, N Composite endpoint, n (%)	11 5 (45.5)	30 10 (33.3)	5 3 (60.0)	29 11 (37.9)	7 4 (57.1)	26 6 (23.1)	9 4 (44.4)	27 7 (25.9)	32 16 (50.0)	112 34 (30.4)

ECD – extended-criteria donors; FAS – full-analysis set; SCD – standard-criteria donors.

Supplementary Figure 1. Incidence of BCAR by Day 168 in patients who received kidneys from ECDs and SCDs (FAS). P values shown are those for ECDs or SCDs across all treatment arms, calculated using the chi-squared test. BCAR – biopsy-confirmed acute rejection; ECD – extended-criteria donor; FAS – full-analysis set; SCD – standard-criteria donor.

Supplementary Table 3. Incidence of treatment-emergent AEs stratified by treatment arm and donor group (FAS).

AEs, n (%)	Arm 1 Immediate-release tacrolimus 0.2 mg/kg/day		Arm 2 Prolonged-release tacrolimus 0.2 mg/kg/day		Arm 3 Prolonged-release tacrolimus 0.3 mg/kg/day		Arm 4 Prolonged-release tacrolimus 0.2 mg/kg/day +basiliximab		Overall				
	293/311 (94.2)		289/309 (93.5)		295/307 (96.1)		270/287 (94.1)		1147/1214 (94.5)				
	ECD n=154	SCD n=155	ECD n=155	SCD n=147	ECD n=153	SCD n=151	ECD n=158	SCD n=125	ECD, Arms 1–4 p value	SCD, Arms 1–4 p value	ECD n=620	SCD n=578	p value
Anemia	63 (40.9)	39 (25.2)	58 (37.4)	45 (30.6)	59 (38.6)	39 (25.8)	64 (40.5)	29 (23.2)	0.9129	0.5416	244 (39.4)	152 (26.3)	<0.0001
Urinary tract infection	47 (30.5)	38 (24.5)	35 (22.6)	35 (23.8)	58 (37.9)	38 (25.2)	46 (29.1)	33 (26.4)	0.0336	0.9671	186 (30.0)	144 (24.9)	0.0523
Diarrhea	42 (27.3)	28 (18.1)	42 (27.1)	27 (18.4)	48 (31.4)	29 (19.2)	44 (27.8)	24 (19.2)	0.8220	0.9921	176 (28.4)	108 (18.7)	<0.0001
Delayed graft function	33 (21.4)	12 (7.7)	30 (19.4)	19 (12.9)	19 (12.4)	16 (10.6)	39 (24.7)	15 (12.0)	0.0470	0.4940	121 (19.5)	62 (10.7)	<0.0001
Edema	33 (21.4)	21 (13.5)	30 (19.4)	23 (15.6)	28 (18.3)	15 (9.9)	26 (16.5)	10 (8.0)	0.7253	0.1930	117 (18.9)	69 (11.9)	0.0010
Creatinine elevation	23 (14.9)	24 (15.5)	23 (14.8)	22 (15.0)	24 (15.7)	21 (13.9)	20 (12.7)	17 (13.6)	0.8865	0.2702	90 (14.5)	84 (14.5)	>0.9999
Hyperglycemia	17 (11.0)	20 (12.9)	23 (14.8)	18 (12.2)	21 (13.7)	24 (15.9)	23 (14.6)	15 (12.0)	0.7555	0.7469	84 (13.5)	77 (13.3)	0.9326
Hyperlipidemia	15 (9.7)	20 (12.9)	14 (9.0)	8 (5.4)	12 (7.8)	10 (6.6)	4 (2.5)	11 (8.8)	0.0587	0.0960	45 (7.3)	49 (8.5)	0.4531

AEs, n (%)	Arm 1 Immediate-release tacrolimus 0.2 mg/kg/day		Arm 2 Prolonged-release tacrolimus 0.2 mg/kg/day		Arm 3 Prolonged-release tacrolimus 0.3 mg/kg/day		Arm 4 Prolonged-release tacrolimus 0.2 mg/kg/day +basiliximab		Overall				
	293/311 (94.2)		289/309 (93.5)		295/307 (96.1)		270/287 (94.1)		1147/1214 (94.5)				
	ECD n=154	SCD n=155	ECD n=155	SCD n=147	ECD n=153	SCD n=151	ECD n=158	SCD n=125	ECD, Arms 1–4 p value	SCD, Arms 1–4 p value	ECD n=620	SCD n=578	p value
Renal impairment	24 (15.6)	14 (9.0)	23 (14.8)	9 (6.1)	29 (19.0)	20 (13.2)	22 (13.9)	12 (9.6)	0.6426	0.2170	98 (15.8)	55 (9.5)	0.0013
Tremor	19 (12.3)	18 (11.6)	21 (13.5)	16 (10.9)	14 (9.2)	18 (11.9)	19 (12.0)	9 (7.2)	0.6730	0.5746	73 (11.8)	61 (10.6)	0.5219
CMV infection	16 (10.4)	10 (6.5)	24 (15.5)	4 (2.7)	25 (16.3)	9 (6.0)	17 (10.8)	5 (4.0)	0.2727	0.4061	82 (13.2)	28 (4.8)	<0.0001
Hypertension	24 (15.6)	21 (13.5)	26 (16.8)	20 (13.6)	16 (10.5)	18 (11.9)	27 (17.1)	10 (8.0)	0.3286	0.4549	93 (15.0)	69 (11.9)	0.1285
Toxic nephropathy	5 (3.2)	7 (4.5)	6 (3.9)	4 (2.7)	12 (7.8)	5 (3.3)	18 (11.4)	6 (4.8)	0.0121	0.7712	41 (6.6)	22 (3.8)	0.0375
PTDM	29 (22.8)*	23 (16.0)†	19 (15.1)‡	11 (8.1)§	22 (17.2)@	22 (15.9)¶	19 (14.4)**	11 (10.1)††	0.2698	0.1178	89 (17.3)‡‡	67 (12.7)§§	0.0455
Ongoing insulin therapy	10 (7.8)*	14 (9.7)†	13 (10.3)‡	8 (5.9)§	18 (14.1)@	9 (6.5)¶	7 (5.3)**	4 (3.7)††	0.0951	0.2765	48 (9.4)‡‡	35 (6.7)§§	0.1108

* n=127; † n=144; ‡ n=126; § n=135; @ n=128; ¶ n=138; ** n=132; †† n=109; ‡‡ n=513, §§ n=526; data are n (%), unless otherwise specified; delayed graft function was defined as dialysis for more than one day within the first week post transplantation; toxic nephropathy was reported as an AE by the investigators. P values across treatment arms within ECD and SCD groups were calculated with the chi-squared test. P values for ECD *vs.* SCD groups were calculated with Fisher's exact test. AE – adverse event; CMV – cytomegalovirus; ECD – extended-criteria donors; FAS – full-analysis set; PTDM – post transplantation diabetes mellitus; SCD – standard-criteria donors.

Supplementary Table 4. Comparison of definitions of ECDs in clinical trials.

Extended-criteria donor characteristics	
United Network for Organ Sharing (UNOS) [14]	• ≥60 years old • 50–59 years with ≥2 of the following conditions: – Death from cerebrovascular accident – Hypertension – Serum creatinine >1.5 mg/dL
ELITE-Symphony [17]	• >60 years old • >50 years with ≥2 of the following conditions: – Death from cerebrovascular accident – Hypertension – Serum creatinine >1.5 mg/dL
OSAKA [9]	• Living or deceased donors • ≥60 years old • 50–60 years with ≥1 of the following conditions: – Death from cerebrovascular accident – Hypertension – Serum creatinine >1.5 mg/dL • Donation after circulatory death

The definition of ECD was calculated retrospectively in the OSAKA study. ECD – extended-criteria donors; OSAKA – <u>O</u>ptimising immuno<u>S</u>uppression <u>A</u>fter <u>K</u>idney transplantation with <u>A</u>dvagraf™; UNOS – United Network for Organ Sharing.

References:

1. Nankivell BJ, Kuypers DRJ: Diagnosis and prevention of chronic kidney allograft loss. Lancet, 2011; 378: 1428–37

2. Gondos A, Döhler B, Brenner H, Opelz G: Kidney graft survival in Europe and the United States: Strikingly different long-term outcomes. Transplantation, 2013; 95: 267–74

3. Lamb KE, Lodhi S, Meier-Kriesche H-U: Long-term renal allograft survival in the United States: A critical reappraisal. Am J Transplant, 2011; 11: 450–62

4. Collins MG, Chang SH, Russ GR, McDonald SP: Outcomes of transplantation using kidneys from donors meeting expanded criteria in Australia and New Zealand, 1991 to 2005. Transplantation, 2009; 87: 1201–9

5. Rao PS, Ojo A: The alphabet soup of kidney transplantation: SCD, DCD, ECD – Fundamentals for the practicing nephrologist. Clin J Am Soc Nephrol, 2009; 4: 1827–31

6. Aubert O, Kamar N, Vernerey D et al: Long term outcomes of transplantation using kidneys from expanded criteria donors: Prospective, population based cohort study. BMJ, 2015; 351: h3557

7. Tedesco Silva H, Yang HHC, Meier-Kriesche H-U et al: Long-term follow-up of a phase III clinical trial comparing tacrolimus extended-release/MMF, tacrolimus/MMF, and cyclosporine/MMF in de novo kidney transplant recipients. Transplantation, 2014; 97: 636–41

8. Ekberg H, Bernasconi C, Tedesco-Silva H et al: Calcineurin inhibitor minimization in the Symphony study: Observational results 3 years after transplantation. Am J Transplant, 2009; 9: 1876–85

9. Albano L, Banas B, Klempnauer JL et al: OSAKA trial: A randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. Transplantation, 2013; 96: 897–903

10. Arns W, Citterio F, Campistol JM: 'Old-for-old' – New strategies for renal transplantation. Nephrol Dial Transplant, 2007; 22: 336–41

11. Isakova T, Xie H, Messinger S et al: Inhibitors of mTOR and risks of allograft failure and mortality in kidney transplantation. Am J Transplant, 2013; 13: 100–10

12. Ferrer F, Mota A, Alves R et al: Renal transplantation with expanded criteria donors: The experience of one Portuguese center. Transplant Proc, 2009; 41: 791–93

13. Lai Q, Pretagostini R, Poli L et al: Delayed graft function decreases early and intermediate graft outcomes after expanded criteria donor kidney transplants. Transplant Proc, 2009; 41: 1145–48

14. Metzger RA, Delmonico FL, Feng S et al: Expanded criteria donors for kidney transplantation. Am J Transplant, 2003; 3(Suppl. 4): 114–25

15. Frutos MA, Sola E, Mansilla JJ et al: Expanded criteria donors for kidney transplantation: Quality control and results. Transplant Proc, 2006; 38: 2371–73

16. La Manna G, Comai G, Cappuccilli ML et al: Prediction of three-year outcome of renal transplantation from optimal donors versus expanded criteria donors. Am J Nephrol, 2013; 37: 158–66

17. Ekberg H, Tedesco-Silva H, Demirbas A et al: Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med, 2007; 357: 2562–75