A paired-kidney allocation study found superior survival with HLA-DR compatible kidney transplants in the Eurotransplant Senior Program

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The Eurotransplant Senior Program (ESP) has expedited the chance for elderly patients with kidney failure to receive a timely transplant. This current study evaluated survival parameters of kidneys donated after brain death with or without matching for HLA-DR antigens. This cohort study evaluated the period within ESP with paired allocation of 675 kidneys from donors 65 years and older to transplant candidates 65 years and older, the first kidney to 341 patients within the Eurotransplant Senior DR-compatible Program and 334 contralateral kidneys without (ESP) HLA-DR antigen matching. We used Kaplan-Meier estimates and competing risk analysis to assess all cause mortality and kidney graft failure, respectively. The log-rank test and Cox proportional hazards regression were used for comparisons. Within ESP, matching for HLA-DR antigens was associated with a significantly lower five-year risk of mortality (hazard ratio 0.71; 95% confidence interval 0.53-0.95) and significantly lower cause-specific hazards for kidney graft failure and return to dialysis at one year (0.55; 0.35-0.87) and five years (0.73; 0.53-0.99) post-transplant. Allocation based on HLA-DR matching resulted in longer cold ischemia (mean difference 1.00 hours; 95% confidence interval: 0.32-1.68) and kidney offers with a significantly shorter median dialysis vintage of 2.4 versus 4.1 yrs. in ESP without matching. Thus, our allocation based on HLA-DR

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matching improved five-year patient and kidney allograft survival. Hence, our paired allocation study suggests a superior outcome of HLA-DR matching in the context of old-for-old kidney transplantation.

Lay Summary

The elderly represent the fastest-growing subpopulation with kidney failure, but only a limited number of such patients receive a kidney transplant in time. Waiting time on dialysis and dialysis vintage are associated with a higher incidence of mortality after a successful kidney transplant. The Eurotransplant Senior Program (ESP) preferentially allocates kidneys from donors aged ≥65 years to elderly recipients aged ≥65 years and successfully expedited the chance for these patients to receive a timely transplant. Elderly patients, however, have a higher risk of kidney allograft rejection as well as infection. "Old-for-old" kidney transplant recipients experience a higher incidence of morbidity and excess mortality. The current allocation study investigated whether matching for human leukocyte antigens (HLAs), in particular HLA-DR, within the ESP program could improve the outcome parameters. We randomly allocated 675 kidneys from donors aged ≥65 years to transplant candidates aged ≥65 years who were on the ESP waiting list. The paired allocation algorithm assigned the first kidney to a patient without mismatches for HLA-DR antigens (i.e., the longest waiting candidate), and the contralateral kidney was allocated following the current ESP standard, based on waiting time only, without matching for HLA antigens. The results showed that allocation based on HLA-DR matching was associated with a 30% lower chance of mortality 5 years after transplantation and with more functioning kidney transplants. This paired allocation study for the first time documented a superior outcome of HLA-DR matching in the context of "old-for-old" kidney transplantation.

T he elderly represent the fastest-growing kidney failure population, with over 50% of the new patients entering renal replacement programs being aged 65 years or older.[1,2] In selected elderly candidates, transplantation adds life-years, and provides better quality of life, and transplanting a kidney of any quality is cost-effective compared to dialysis.[3–8] However, only a minority of elderly patients with kidney failure are eventually listed for transplantation.[1] Along with the ongoing shortage of organs available for transplantation, elderly transplant candidates face another critical disadvantage. Not only is waiting time while on dialysis associated with significant mortality incidence, but also, dialysis vintage reduces graft survival and overall life expectancy after transplantation.[9,10]

Some degree of intuitive age matching, including "old-for-old" allocation, has always been part of clinical decision-making in most Western countries. Worldwide, the first initiative to expedite the chance for elderly patients to receive a kidney transplant was the Eurotransplant Senior Program (ESP) initiated more than 20 years ago. Preferential allocation of kidneys from donors aged ≥65 years to elderly recipients aged ≥65 years (old-for-old) significantly increased the chance of receiving a timely transplant.[11]

A serious threat to older kidney transplant recipients is the excess mortality incidence due to infectious causes, which is the consequence of overimmunosuppression in the light of an already senescent immune system.[12–14] In addition, recipients of kidneys from older donors experience more acute rejection episodes within every recipient age-category.[15–17] Kidneys from older donors are more vulnerable to both cellular and humoral rejection mechanisms and carry an increased risk of graft failure.[18–20] Although expanded-criteria donor kidneys have been reported to provide, on average, 5 added years of life in general,[21] additional courses of high-dose corticosteroids and/or T cell–depleting antibodies may substantially increase the incidence of infectious morbidity and mortality in elderly recipients. In fact, although the 5-year analysis of the ESP data has documented acceptable kidney graft survival results, the incidence of infection-related mortality was approximately 30%—that is, quite high.[11,22]

Current ESP allocation preferentially allocates kidneys from older donors (aged ≥65 years) without prospective human leukocyte antigen (HLA) matching, to older (aged ≥65 years) local transplant candidates. Historically, the minimal standard of allocation within Eurotransplant has been at least a 2 DR or 1 B/1 DR match for HLA antigens. To reduce immunogenicity within ESP, the kidney advisory board advised that the ESP allocation algorithm be temporarily changed to include HLA-DR matching. The current study evaluated clinical outcomes of paired kidney allocation with or without matching for HLA class-II antigens within the context of ESP kidney transplantation.

METHODS
Study population and allocation
Between January 1, 2010 and January 4, 2014, a total of 675 recipients, aged ≥ 65 years, received a kidney via the paired Eurotransplant Senior DR-compatible Program (ESDP)/ESP kidney allocation algorithm. Only kidneys donated after brain death (DBD) were allocated per donor, with the first kidney being given to the longest waiting patient on the list with a zero HLA-DR mismatch (ESDP). The contralateral kidney was allocated according to the current ESP policy, which is allocation by waiting time only, without consideration of HLA-matching. Matching for HLA-DR was performed at the split antigen level, except for HLA-DR3, for which matching was performed at the broad antigen level. HLA-DR and -DQ typing was performed by using sequence-specific oligonucleotide (SSO) and sequence-specific primer (SSP) DNA-based

techniques. For all the patients and donors included, a typing result for the HLA-DR locus was present, and for $\geq 90\%$, a result for HLA-DQ was present. HLA-DR3 could not be split in HLA-DR17/DR18. In this paired allocation study of donor kidneys with or without matching for HLA-DR antigens, the recipients' characteristics, transplant-specific parameters, and outcome parameters were collected independently. Allocation was on 6 HLA antigens (A, B and DR; not including HLA-DQ or -DP). The allocation script further included identical ABO blood groups and stratification for male or female donor as well as left or right kidney, while keeping cold ischemia time as short as possible but always under 20 hours.

The change in the standard ESP allocation protocol to include the ES(D)P algorithm was proposed by the Eurotransplant Kidney Advisory Committee, based on the results of the 5-year analysis of the ESP.[11] The algorithm was set up to evaluate the need to reintroduce the previous standard of (at least minimal) matching for HLA antigens, the founding principle of kidney exchange within the Eurotransplant region. The decision was made by the international board, in close cooperation with the relevant regulatory authorities in the participating countries.

Only nonimmunized ($\leq 5\%$ panel-reactive antibodies) recipients waiting for a first kidney transplant and negative cellular cross-match before transplantation were included in the allocation algorithm. Participation did not interfere with the choice of treatment, sample collection, or medical procedures, which entirely followed standard hospital practice. The power calculation was based on the increased (treated) acute rejection rate observed in the 5-year ESP analysis.[11] To detect a 10% reduction with 80% power required allocation of at least 251 kidneys per arm. Numerous legal and logistic restrictions, however, made a trial design with rejection as the primary endpoint (including uniform clinical immunosuppression and central monitoring of biopsy-confirmed acute rejection) not feasible. We therefore concentrated on the mandatory allocation and survival data as captured by a dedicated coworker within the ESP registry. These reports do not include standard or certified data on acute rejection and estimated glomerular filtration rate. In parallel, the ESP program continued allocation of single DBD kidneys from elderly donors or donation-after-circulatory-death (DCD) donors to ESP candidates, including those with panel-reactive antibodies and/or repeat transplants.

Data source and ethical approval
Donor characteristics: age, sex, history of hypertension or diabetes, cause of death, intensive care unit stay, serum creatinine level, procurement procedure, HLA-typing, cold ischemia time, and recipient information (age, sex, cause of kidney failure, date of first dialysis, HLA-typing, panel reactive antibody status) were retrieved from the Eurotransplant Information System. Participation in the registry is mandatory, and next to baseline donor and recipient characteristics, follow-up data are collected annually for every kidney transplant (date of kidney graft failure and return to dialysis or patient death). During the paired kidney allocation period, a dedicated study coordinator collected and verified the data on patient and graft survival by means of phone calls once every 3 months to the participating transplant centers in 4 countries. The predefined follow-up period was 5 years. Patients were censored in cases in which loss to follow-up or end of follow-up (December 16, 2019) occurred. After the most recent annual ESP update—December 14, 2022—<2% of transplant recipients were lost to follow-up at 5 years. The study was approved by the medical ethical committee of the Leiden University Medical Center and the relevant authorities

and organ procurement organizations in the participating ESP countries (Austria, Belgium, Germany, Netherlands). Patients provided written consent for the participation in the ESP/ESDP program.

Outcome parameters
Survival of the patient was defined as the time from transplantation until death. Mortality (with or without graft function) was ascertained at the transplant-center level by annual survey. Kidney graft failure was defined by return to dialysis (or a repeat transplantation). Primary nonfunction was defined as failure of the graft to ever function, irrespective of cause. Dialysis vintage was defined by the waiting time while on dialysis until transplantation, starting at the first day of dialysis initiation. The kidney donor–risk index (KDRI; with the following parameters: race, donor age, weight, height, hepatitis C virus antibodies, hypertension, diabetes, deceased brain-death donor) was used as a surrogate for quality of the deceased-donor organ.[21]

Statistical analysis
Univariable comparisons between the ESDP and ESP group were done using χ^2 tests for categorical data, and *t* tests or Wilcoxon tests for parametric continuous and nonparametric continuous data, respectively. We used the Kaplan–Meier method to calculate the overall mortality incidence. We assessed the cause-specific risk of kidney graft failure using the competitive risk-analysis method (R statistics "survival" software package version 1.4.2; R Foundation). The *P* values were determined by log-rank test. Cox proportional hazards regression with list-wise deletion and forward selection (entry $P = 0.05$; removal $P = 0.10$), according to the standard SPSS (IBM) algorithm, was used to add covariables for multivariable analyses. We considered 2-sided *P* values <0.05 to be statistically significant. These analyses were performed using SPSS 25.0 (IBM Corp.).

RESULTS
Allocation, donor, and recipient characteristics
A total of 675 kidney transplant procedures were performed during the period of paired allocation within ESP; 341 kidneys were allocated with a zero HLA-DR mismatch (ESDP), and 334 kidneys were allocated according to waiting time, without HLA-DR matching, to ESP recipients (Supplementary Figure S1A). Five-year follow-up data were missing for 8 ESP recipients (2.4%) and 5 ESDP recipients (1.5%), respectively (Supplementary Figure S1B). In total, 662 patients were included in the complete case analysis. Almost 90% of kidneys were allocated in pairs. From 38 donors, only one kidney was transplanted, 22 were allocated via ESP, and 18 were allocated via ESDP. From 12 kidney donors, both kidneys were allocated to a DR-compatible recipient, and in 7 donors, both kidneys were allocated to ESP. Demographic and clinical characteristics of kidney donors and recipients are summarized in Table 1. Per the allocation algorithm, donor characteristics were paired, and all ESDP patients received a zero HLA-DR mismatched kidney. Likewise, the waiting time or median dialysis vintage (4.1 vs. 2.6 years) was significantly longer in the ESP group ($P < 0.0001$). The allocation strategy with HLA-DR matching resulted in a longer median cold ischemic time (12.0 hours [interquartile range {IQR}: 9.4–15.1) versus

Table 1 | Allocation of paired kidneys within ESP by matching for HLA-DR antigens

Characteristic	ESDP (n = 336)	ESP (n = 326)	P
Allocation			
HLA-mismatch			
DR 0/1/2	100/0/0[a]	0/49/51	
B 0/1/2	5/44/51	1/32/67	
A 0/1/2	13/55/32	12/44/44	
Waiting time/dialysis vintage, yr	2.6 (1.8–4.0)[a]	4.2 (2.8–5.5)	
Categorical, yr			
<2	30	13	
2–5	58	54	
>5	12	33	
Cold ischemia, h	12 (9–15)[a]	11 (8–13)	
Donor			
Age, yr	71 (68–74)	71 (68–74)	0.58
Sex, female	57	56	0.88
Cause of death			0.93
CVA	46	45	
SAB	22	25	
Trauma	12	13	
Anoxia	7	6	
Brain tumor	3	4	
Other/unknown	10	7	
Hospital stay, d	5 (2–7)	5 (2–7)	0.87
Creatinine, μmol/l	84 ± 45	85 ± 49	0.69
Kidney, left	50	50	0.94
KDRI score			0.95
1.00–1.49	19	18	
1.50–1.99	55	56	
≥2.00	26	26	
Recipient			
Age, yr	69 (67–72)	69 (66–72)	0.24
Sex, male	71	72	0.67
Native kidney disease			0.98
Glomerular/immunologic	27	31	
Diabetes/hypertension/vascular	25	25	
Congenital/hereditary	13	12	
Tubulointerstitial/pyelonephritis	6	5	
Other	12	11	
Unknown	17	17	
Preemptive transplant	3	1	0.11

CVA, cerebrovascular accident; ESP, Eurotransplant Senior Program; ESDP, Eurotransplant Senior DR-compatible Program; HLA, human leukocyte antigen; KDRI, kidney donor risk index; SAB, subarachnoidal bleeding.
[a]P < 0.0001.
Values are %, median (interquartile range), or mean (±SD), unless otherwise indicated.

10.6 hours (IQR: 7.9–13.4) in ESDP and ESP (P < 0.0001), respectively. Of note, 50% of patients in the ESP arm of the allocation scheme received a kidney with 1 HLA-DR mismatch. Allocation within the ESP program is ABO-identical by default (ABO-O 54%; ABO-A 39%; ABO-B 6%; ABO-AB 1%). For this temporary change with paired allocation within the ESP program, only nonimmunized candidates panel reactive antibodies (PRA) <5% listed for a first kidney transplant were considered. Recipient and transplant characteristics were similar in the 2 groups.

Although female patients appeared to be somewhat under-represented, the differences were minor, compared to all ESP candidates. Before initiation of the paired allocation within ESP (December 31, 2009), a total of 2131 candidates were listed in ESP. Among the 50% of candidates on the active waiting list, 88% were nonimmunized, with 67% being male and 33% female. Near the end (December 31, 2013), the corresponding numbers were 84%, 66%, and 34%, respectively. Although the percentage of immunized patients on the active waiting list increased between December 2009 and December 2013, from 12.2% to 16.4%, the proportion of female patients decreased from 60% to 53%. The incidences of primary nonfunction (4.9% vs. 6.4%) and delayed function were comparable in the ESDP and ESP recipients. Detailed information on the incidence of acute rejection and kidney function was not available. Initial immunosuppression showed the use of induction in 64% of patients (basiliximab in 93% of cases), and triple maintenance therapy consisting of steroids, calcineurin inhibitors (tacrolimus 69%), and mycophenolate (99%).

Survival analysis

Allocation of paired kidneys with a zero HLA-DR mismatch was associated with a significantly lower chance of mortality 5 years after transplantation (log-rank P < 0.005). The 5-year Kaplan–Meier estimates for (all-cause) mortality are plotted in Figure 1a. Besides a zero HLA-DR mismatched kidney transplant (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.53–0.95, P < 0.05), recipient age, end-stage (native) kidney failure due to arterial hypertension or diabetes, and return to dialysis in the first year post-transplant were independently associated with 5-year mortality (Table 2). The impact of kidney graft failure and return to dialysis in the first year after transplantation on 5-year mortality in this cohort of elderly transplant recipients is illustrated in Supplementary Figure S2.

The 5-year incidences of kidney graft failure are plotted in Figure 1b. The cause-specific hazards for kidney graft failure for allocation with a zero HLA-DR mismatched at 1 year and 5 years post-transplant were 0.55 (95% CI 0.35–0.87; P < 0.01) and 0.73 (95% CI 0.53–0.99; P < 0.05), respectively (Tables 3 and 4). At 1-year allocation with a zero HLA-DR mismatch, donor as well as recipient age was associated with kidney graft failure. Multivariable analysis revealed the KDRI to be a parameter that was associated with 5-year kidney graft failure. The paired kidney allocation algorithm selected only DBD donors, first transplants, and no hepatitis C virus–positive candidates' antibodies were transplanted. The majority (approximately 75%) of patients received a kidney with a KDRI score less than 2 (Table 1). In this subgroup, the beneficial impact of a zero HLA-DR mismatched kidney was evident (log-rank P < 0.05; Figure 2) and was most pronounced in the first year after transplantation (log-rank P = 0.015). Beyond the first year, the adverse impact of a higher KDRI score remained, but a beneficial effect of the allocation with a zero HLA-DR mismatch was no longer observed (Table 4).
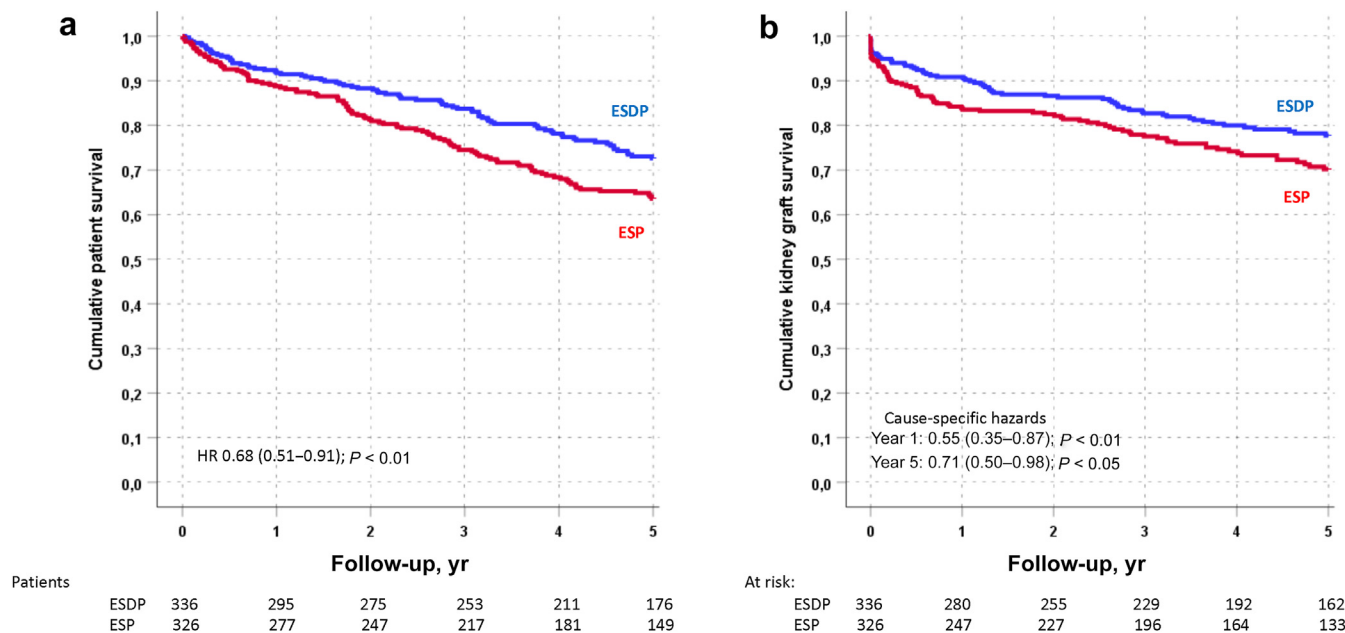
Figure 1 | (a) Five-year (all-cause) mortality (Kaplan-Meier estimates, $P < 0.01$, hazard ratio [HR] 0.68 (95% confidence interval [CI] 0.51–0.91) and **(b)** kidney graft failure with cause-specific hazards at 1-year: HR 0.55 (95% CI 0.35–0.87); $P < 0.01$ and at 5 years: HR 0.71 (95% CI 0.52–0.98); $P < 0.05$, according to allocation of paired kidneys with (Eurotransplant Senior DR-compatible Program [ESDP]) or without (Eurotransplant Senior Program [ESP]) matching for human leukocyte antigen (HLA)–DR antigens. Parentheticals give 95% CI.

Waiting time/dialysis vintage

Allocation in ESP is primarily directed by waiting time while on dialysis. Dialysis vintage was 4.1 years (IQR 2.81–5.49) with the ESP scenario, versus 2.6 years (IQR 1.85–3.96) via ESDP ($P < 0.00005$; Table 1). The proportion of patients who received a transplant within 5 years after initiation of dialysis was 88% in the ESDP group, versus less than 67% for ESP (Table 1). The ESDP scenario resulted in significantly more transplants in elderly patients who spend less than 2 years on dialysis (30% vs. 13% in ESP; $P < 0.0001$). The cumulative incidences in kidneys offered and transplanted, by waiting time, are plotted in Figure 3a. Median waiting times were

different in Austria, Belgium, Germany, and Netherlands, but the cumulative incidences of elderly kidney transplants by dialysis vintage remained comparable over the years of allocation (Figure 3b). By principle, the ESP selected patients based on longest waiting time, resulting in 33% of kidneys being allocated to elderly recipients with a dialysis vintage over 5 years versus only 13% in the ESDP scenario (zero HLA-DR mismatched, followed by the longest waiting time). Cumulative incidences of mortality by dialysis vintage, according to allocation with or without HLA-DR mismatch, are plotted in Figure 3. No significant differences were found for waiting times up to 5 years. Beyond a 5-year dialysis vintage,

Table 2 | Five-year mortality

Factor	Hazard ratio (95% CI)			
	Univariable	P	Multivariable	P
Allocation				
Allocation via ESDP vs. ESP	0.69 (0.52–0.92)	<0.05	0.71 (0.53–0.95)	<0.05
Dialysis vintage, yr	1.09 (1.01–1.17)	<0.05	1.07 (1.01–1.17)	<0.05
HLA-class-I mismatch	1.03 (0.89–1.21)	0.68		
Donor age, yr	1.01 (0.98–1.04)	0.77		
Donor sex, M/F	0.88 (0.66–1.18)	0.39		
Cold Ischemia, h	1.00 (0.97–1.03)	0.96		
Recipient				
Age, yr	1.04 (0.99–1.09)	<0.01	1.07 (1.02–1.11)	<0.01
Sex, M/F	1.02 (0.73–1.43)	0.89		
ESRD: hypertension or diabetes	1.40 (1.00–1.94)	<0.05	1.49 (1.07–2.09)	<0.05
Return to dialysis in first year	3.46 (2.38–5.02)	<0.0001	3.33 (2.28–4.86)	<0.0001

CI, confidence interval; ESDP, Eurotransplant Senior DR-compatible Program; ESP, Eurotransplant Senior Program; ESRD, end-stage renal disease; F, female; HLA, human leukocyte antigen; M, male.

Table 3 | One-year kidney graft failure (death-censored)

	Hazard ratio (95% CI)			
Factors	Univariable	*P*	Multivariable	*P*
Allocation				
Allocation via ESDP vs. ESP	0.55 (0.35–0.87)	<0.05	0.59 (0.38–0.93)	<0.05
Dialysis vintage, yr	1.13 (1.02–1.25)	<0.05	1.08 (0.97–1.21)	0.15
Donor age, yr	1.06 (1.02–1.11)	<0.01	1.06 (1.02–1.11)	<0.01
KDRI score				
1.00–1.49	1		1	
1.50–1.99	2.00 (0.94–4.23)	0.07	1.81 (0.83–3.94)	0.13
≥2.00	2.52 (1.14–5.54)	<0.05	1.84 (0.71–4.73)	0.21
Donor sex, M/F	0.89 (0.57–1.38)	0.59		
HLA-class-I mismatch	1.19 (0.93–1.52)	0.17		
Cold ischemia, h	0.98 (0.93–1.03)	0.41		
Recipient				
Age, yr	0.92 (0.86–0.98)	<0.05	0.92 (0.86–0.99)	<0.05
Sex, M/F	1.00 (0.71–1.43)	0.98		
Kidney failure (hypertension or diabetes vs. other causes): AHT or DM	1.26 (0.78–2.04)	0.35		

AHT, arterial hypertension; DM, diabetes mellitus; CI, confidence interval; ESDP, Eurotransplant Senior DR-compatible Program; ESP, Eurotransplant Senior Program; F, female; HLA, human leukocyte antigen; KDRI, kidney donor risk index; M, male.

the cumulative incidences of kidneys offered and transplanted were similar (Supplementary Figure S3). Allocation with a zero HLA-DR mismatch according to ESDP, however, was associated with a significantly lower chance of mortality (Figure 3). No differences were present in candidate age, cause of their kidney failure, or in the donor age or KDRI score of the kidneys offered. Return to dialysis within the first postoperative year occurred significantly less frequently in those who received a kidney transplant w/o HLA-DR mismatches. The beneficial effect of a zero mismatched kidney on kidney graft failure in the context of the KDRI score is plotted in Figure 4.

DISCUSSION

The introduction of the ESP allocation program has significantly improved the chances that elderly waitlisted dialysis patients will receive a timely transplant. Although the majority of patients entering renal replacement programs are over the age of 65 years, or even 75 years, elderly patients who are placed on the waiting list represent a highly selected subgroup of transplant candidates.[23] In this paired kidney allocation study, we investigated for the first time the effect of HLA-DR matching on outcome within the ESP. The inclusion of prospective matching for HLA-DR antigens in the allocation algorithm was associated with a 30 percent lower chance

Table 4 | Kidney graft failure (censored): 5 years

	Hazard ratio (95% CI)			
Factors	Univariable	*P*	Multivariable	*P*
Allocation				
Allocation via ESDP vs. ESP	0.71 (0.52–0.98)	<0.05	0.73 (0.53–0.99)	<0.05
Dialysis vintage, yr	1.03 (0.96–1.13)		1.06 (0.98–1.15)	0.16
Donor age, yr	1.06 (1.03–1.09)	<0.0005	1.03 (0.99–1.08)	0.16
KDRI score				
1.00–1.49	1		1	
1.50–1.99	2.04 (1.18–3.54)	<0.05	1.85 (1.05–3.26)	<0.05
≥2.00	2.88 (1.62–5.12)	<0.0005	2.17 (1.08–4.36)	<0.05
Donor sex, M/F	0.82 (0.59–1.14)	0.24		
HLA-class-I mismatch	1.03 (0.87–1.23)	0.73		
Cold ischemia, h	1.01 (0.98–1.04)	0.54		
Recipient				
Age, yr	0.97 (0.92–1.02)	0.20		
Sex, M/F	1.00 (0.71–1.43)	0.98		
Kidney failure (hypertension or diabetes vs. other causes): hypertension/diabetes	1.24 (0.87–1.78)	0.24		

CI, confidence interval; ESDP, Eurotransplant Senior DR-compatible Program; ESP, Eurotransplant Senior Program; F, female; HLA, human leukocyte antigen; KDRI, kidney donor risk index; M, male.
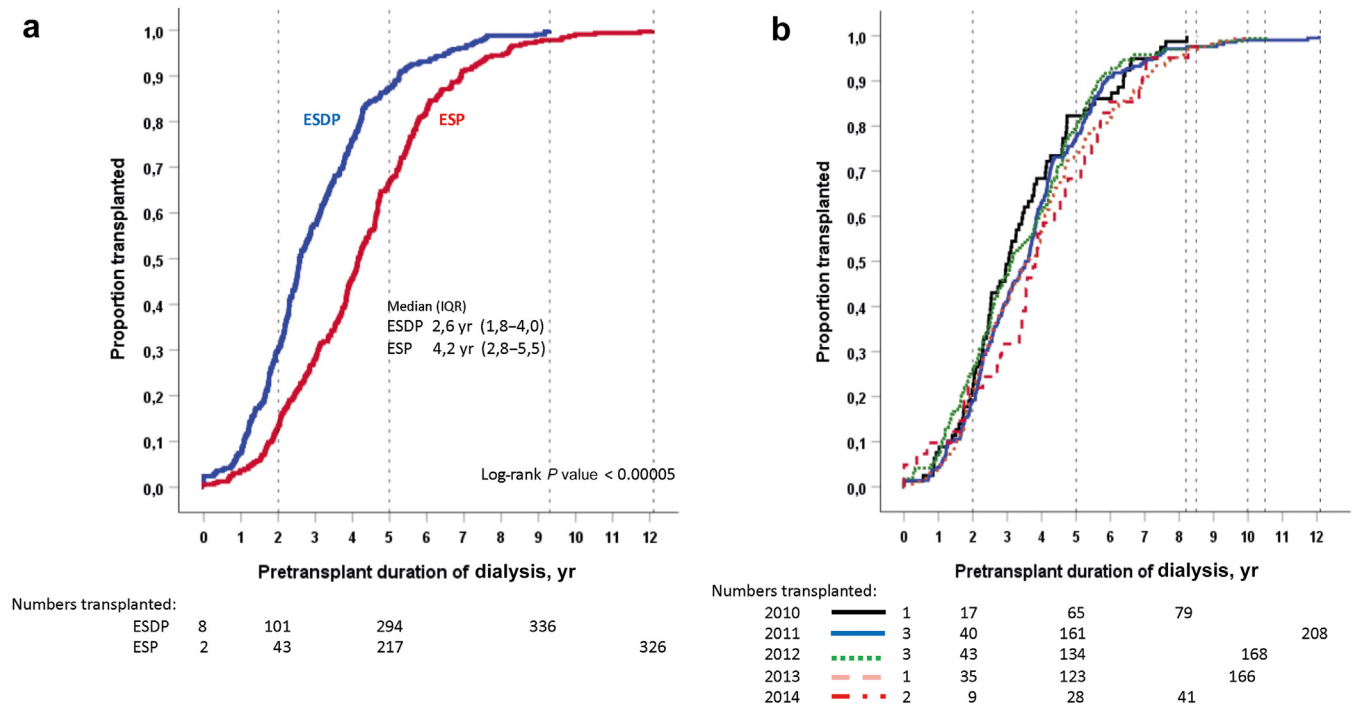
Figure 2 | Cumulative incidence of transplanted candidates by dialysis vintage according to (a) allocation of paired kidneys with (Eurotransplant Senior DR-compatible Program [ESDP]) or without (Eurotransplant Senior Program [ESP]) matching for human leukocyte antigen (HLA)–DR antigens and (b) by calendar year. IQR, interquartile range.

of mortality 5 years after transplantation and more functioning kidney transplants. In particular, 1-year death-censored kidney graft survival was significantly better and could eventually explain a lower mortality incidence, as return to dialysis in the first post-transplant year was an important determinant for patient death after 5 years.

The allocation algorithm based on HLA-DR matching resulted in a shift in waiting time, with significantly more recipients receiving a kidney offer within the first 2 years after initiation of dialysis. Of importance, the benefit of prospective HLA-DR matching was independent of other factors that were associated with all-cause mortality, including dialysis vintage.
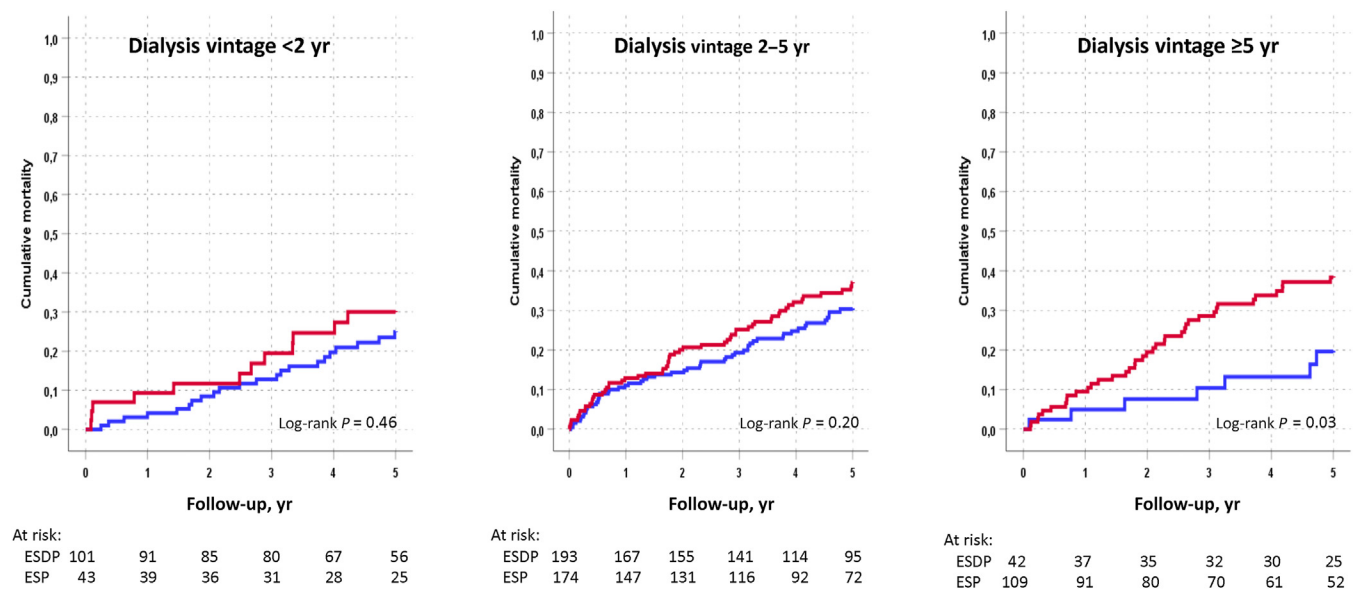

Figure 3 | Five-year (all-cause) mortality by dialysis vintage (<2 year; 2–5 years; ≥5 years) according to allocation of paired kidneys with (Eurotransplant Senior DR-compatible Program [ESDP]) or without (Eurotransplant Senior Program [ESP]) matching for human leukocyte antigen (HLA)–DR antigens.

Patients at risk:

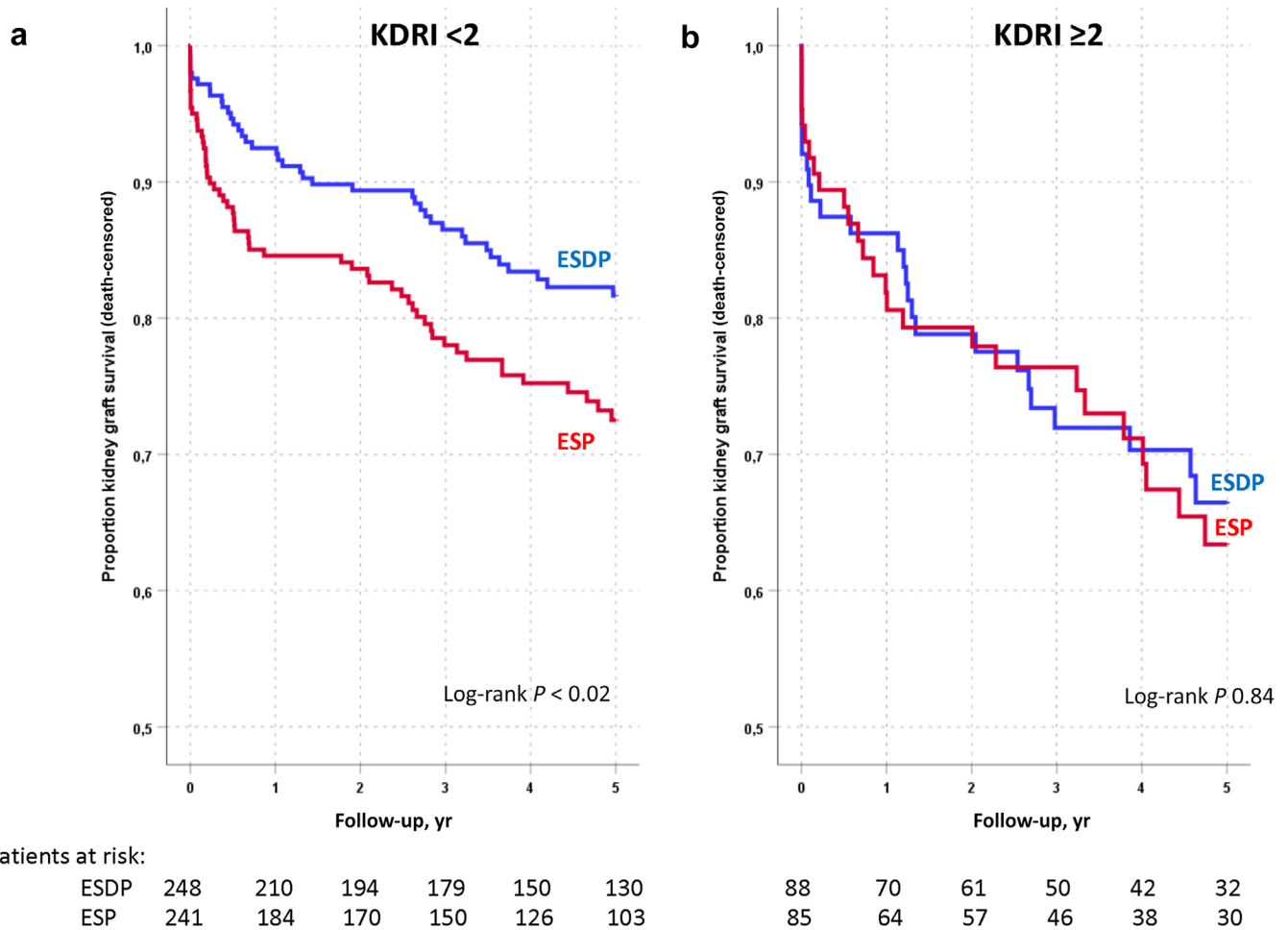|												
ESDP	248	210	194	179	150	130	88	70	61	50	42	32
ESP	241	184	170	150	126	103	85	64	57	46	38	30

Figure 4 | Kidney graft failure by initial quality assessment (a) kidney donor risk index (KDRI) score <2 and (b) KDRI score ≥2 according to allocation of paired kidneys with (Eurotransplant Senior DR-compatible Program [ESDP]) or without (Eurotransplant Senior Program [ESP]) matching for human leukocyte antigen [HLA]-DR antigens.

Return to dialysis in the first post-transplant year was strongly associated with excess 5-year mortality, with comparable hazards in recipients of kidneys allocated with versus without HLA-DR matching. Kidney allograft failure in the context of old-for-old allocation may have immunologic and nonimmunologic determinants or both. First, it has become widely accepted that recipients of older kidneys experience higher acute rejection rates within each recipient age category.[15–17,20] Episodes of T cell–mediated acute rejection are associated with histo-incompatibility, and in particular, the degree of mismatching for HLA-DR antigens.[18,19]

Although we were unable to retrieve detailed information on acute rejection from the registry, the large majority of acute rejection episodes in this (nonimmunized) cohort of older first kidney–transplant recipients of low to standard immunologic risk were most likely Tcell–mediated. These episodes generally respond well to standard rejection treatment strategies, but functional consequences or reversibility may also depend on the tissue quality of the kidney transplanted. In this cohort of kidney donors with a median donor age of 72 years, histocompatibility for HLA-DR antigens resulted in significantly better 1-year kidney allograft survival. In particular, a more pronounced benefit was found in recipients of kidneys with KDRI scores below 2. The large majority of the patients received a kidney graft with a KDRI score of less than 2. Thus, these results support the principal benefit of preventing acute rejection by histocompatibility, and the need of additional courses of high-dose corticosteroids and/or T cell–depleting antibodies, which result in excess infection-related morbidity and mortality, especially in the elderly. Acute rejection may be adequately treated, but functional reversibility in vulnerable kidneys is likely to be incomplete, while increasing the risk of infection-related mortality. Indeed, although the 5-year analysis of the ESP data has documented quite acceptable kidney graft survival rates, the rejection rate was 5%–10% higher, and mortality due to infections was 30%, which is quite high.[11]

By default, the ESP program candidates are selected according to their having an identical ABO blood group and their cumulative waiting time (i.e., dialysis vintage) starting the day of first dialysis. Consequently, a significant

proportion of kidneys in the different countries were offered to candidates with a dialysis vintage of over 5 years. The uniform finding in recent literature has been that dialysis vintage has a consistently impact on patient survival and uncensored graft survival.[10,24] In addition, with time, candidates may experience more frequent (temporary) delisting (or may die) before a kidney becomes available. The use of HLA-DR compatibility as the principal selection parameter resulted in a significant shift in the median dialysis vintage, and in significantly more kidneys being offered to recipients with a dialysis vintage of less than 2 years (Table 1). More than one explanation for this observation may be possible, but the most plausible in our opinion is as follows. The chance of a receiving a kidney offer is most likely a direct reflection of the relative ABO blood group and the HLA class-II allele or haplotype frequencies in the background population of both recipients and potential kidney donors. Finding a zero mismatch between donor and recipient is facilitated by significantly less polygenic and polymorphic characteristics of HLA-DR, as compared to HLA class-I molecules. Such a "reset" by the allocation policy is supported by at least the observation that differences in waiting time with or without prospective matching for HLA-DR antigens occurred within the first year of randomized allocation and structurally overruled waiting time in the following years. A better match with an earlier transplant reduces the chance of being (temporarily) delisted for those candidates and of not receiving a kidney offer. Given that transplant numbers in this selected pool of elderly candidates are not increasing, the impact of delisting is likely to remain constant, but it may include factors such as sex and/or sensitization. Overall, we found similar delisting parameters for male patients and female patients, and/or immunization. A detailed evaluation of (temporary) delisting that includes all male and female ESP patients, as well as transplant candidates of minority ethnic groups, is beyond the scope of this article.

The current study also has limitations. In this analysis of registry data, we did not have complete and detailed information regarding the occurrence of acute rejection episodes, rejection treatment(s), or evolution of renal allograft function. Second, we cannot determine from this study whether female patients who are immunized or transplant candidates of minority ethnic groups will be disadvantaged by this strategy. In parallel, the ESP program continued to allocate single kidneys from elderly donors (DBD or DCD) to ESP candidates, immunized or not, and/or repeat transplant candidates.

In conclusion, this paired kidney allocation algorithm within the ESP documented an independent beneficial effect of HLA-DR matching on the incidences of both mortality and functioning kidney grafts in the context of old-for-old kidney transplantation. In addition, kidney allocation based on HLA-DR matching resulted in a small increase in cold ischemia and shorter dialysis duration.

APPENDIX
Members of the Eurotransplant Senior DR-compatible Program (ESDP) Study Group

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DISCLOSURE

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary Figure S1. (**A**) Flow chart of the paired allocation algorithm within the Eurotransplant Senior Program. (**B**) Transplant recipients included in the follow-up analyses.
Supplementary Figure S2. Cumulative incidence of (all-cause) mortality in "old-for-old" kidney transplant recipients, stratified by death with functioning kidney graft or return to dialysis within the first post-transplant year.
Supplementary Figure S3. Kidneys transplanted by dialysis vintage <5 or ≥5 years according to allocation of paired kidneys with (Eurotransplant Senior DR-compatible Program [ESDP]) or without (Eurotransplant Senior Program [ESP]) matching for human leukocyte antigen (HLA)–DR antigens.

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