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ORIGINAL ARTICLE

Rescue allocation and recipient oriented extended allocation in kidney transplantation—influence of the EUROTRANSPLANT allocation system on recipient selection and graft survival for initially nonaccepted organs

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SUMMARY

Nonaccepted kidneys grafts enter the rescue allocation (RA) process to avoid discards. In December 2013, recipient oriented extended allocation (REAL) was introduced to improve transparency. The aim of this study was to evaluate the influence of REAL on recipients′ selection and graft function compared to the formerly existing RA as well as to identify factors that influence graft outcome. Therefore, a multicenter study of 10 transplant centers in the same region in Germany was performed. All transplantations after RA or REAL from December 1, 2012, until December 31, 2014, with a follow-up time until December 31, 2015 were analyzed. 113 of 941 kidney transplantations were performed after RA or REAL (12%). With REAL, the number of refusals before transplantation had increased (12 ± 7.1 vs. 8.6 ± 8.6, $P = 0.036$), and cold ischemia time has decreased (13.6 ± 3.6 vs. 17.2 ± 4.8 h, $P = 0.019$). Recipients after REAL needed significantly more allocation points compared to RA to receive a kidney. One-year graft survival was comparable. If kidneys from the same donor were transplanted to two recipients at one center, the greater the difference in recipient age, the greater the difference in serum creatinine after 12 months (-0.019 mg/dl per year, $P = 0.011$) was, that is older recipients showed lower creatinine. REAL influences selection of the recipients compared to the former RA era for successful organ receipt. Graft function is comparable and seems to be influenced by recipient age.

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Introduction

3169 kidney transplantations had been performed in the Eurotransplant (ET) region [1] in 2015 facing 10 400 patients active on the waiting list. This obvious deceased donor organ shortness warrants optimal use of the available organs. During the standard allocation procedure (SAP), the ranking of a designated recipient is determined by age, medical urgency, %PRA level, HLA-matching between donor and recipient, waiting time, and donor region. Based on these parameters, an allocation score is calculated and a match list is generated [2]. However, organs allocated by the SAP but finally not accepted enter subsequent allocation protocols to avoid discards. Organ quality or medical recipient-related reasons are among the leading causes of nonacceptance [3]. Thus, the allocation system should be refined to minimize discard rates of these organs. The number of kidney grafts in the ET region allocated by nonstandard allocation continually increased during the last years from 6% in 2011 to 11% in 2015 [1]. To prevent loss of organs, deviation from the SAP is necessary and useful. Until November 2013, the so-called rescue allocation (RA) took place: RA was initiated in case of a 5 times nonacceptance of a renal graft for medical reasons during the SAP. In this case, the allograft was offered to all centers in the region of the procurement (first-line RA, noncompetitive) [4]. If all centers had declined acceptance of the allograft again, a competitive center allocation in the greater area of procurement was initiated (second-line-RA). During RA, centers were free to choose any recipient from their waiting list for transplantation of the “rescue organ”. To increase transparency in the selection of the designated recipients, ET introduced the “recipient oriented extended allocation” (REAL) [2] in December 2013: A center-based match list according to the original ranking of the recipients in the SAP is offered to each regional transplant center via an online application. From this list, two recipient candidates may be chosen by the center. The organ will then be offered to the highest ranked recipient chosen by any of the centers. If REAL also fails, a competitive RA is started, where the regional centers are free to choose any recipient from their center-based waiting list without preselection by ET [4]. The establishment of RA led to discard rates for donated kidneys of 7.5% [5]. The 1-year graft survival with 77% for kidneys from this special group seemed to be acceptable [3] assuming that each of these organs is chosen for its suitable recipient. In the past, the huge advantage of RA was the chance to shorten the waiting time for the designated recipient compared to the SAP (34% of recipients on the ET waiting list and 44% in Germany have a waiting time >5 years [1]). We hypothesize that REAL could have an influence on waiting time. At present, no data exist that analyzes the effects of REAL. Currently, it is unresolved who will benefit from REAL or which kind of kidney grafts after REAL/RA should really be discarded. To analyze the advantages of REAL/RA, the “Working Group NRW Transplant Physicians”, a union of all eight kidney transplant centers in the state of North Rhine-Westphalia, Germany (17.5 Mio inhabitants, 27% of all kidney transplantations in Germany), and four associated German transplantation centers, with the purpose to synchronize processes in renal transplantation and living kidney donation, performed a multicenter study analyzing REAL/RA data. This study included all kidney transplantations performed in 10 centers from DBD-donors allocated via RA or REAL from December 2012 until December 2014 with a minimum follow-up of 1 year. The aim of this study was to evaluate the influence of REAL on recipients′ selection and graft function in comparison with the formerly existing RA as well as to identify factors that influence the outcome after REAL and RA.

Patients and methods

Ethics

Institutional review board approval was obtained for the study by the ethics committee of the medical faculty of the University of Cologne (No 15-023) and adopted by the participating centers. The study followed national laws and guidelines and the Declarations of Helsinki and Istanbul.

Study design

The study was designed as a multicenter study with 10 participating German transplant centers (Aachen, Bochum, Bonn, Düsseldorf, Essen, Kiel, Köln-Lindenthal, Köln-Merheim, Lübeck, and Münster). Data for the study were collected and analyzed at the end of the follow-up time. The study period was December 1, 2012, until 31 December 31, 2014, with a follow-up time until December 31, 2015 (minimum 12-month follow-up for every recipient, REAL was introduced at December 9, 2013). First, all transplantation procedures with deviation of the standard allocation scheme (RA or REAL) of the participating kidney transplant centers were extracted from the ET database. Then, the baseline characteristics of these procedures were transferred into the pseudonominized study database. After the end of follow-up time, the participating transplant centers provided the pseudonominized follow-up data using electronic case report forms, which were entered into the study database and analyzed. In total, 122 items (see Appendix S1 for eCRF) were obtained for each procedure. The main outcome of the study was graft function (serum creatinine) after 1 year. No data sets had been excluded from final statistical analysis.

Statistical methods

Qualitative data were summarized by count (percentage) and quantitative data by mean ± standard deviation or median (interquartile range), contingent on the presence of skewness/outliers. Location differences between groups were evaluated by Student's t-test or the Wilcoxon rank sum test, dependent on distributional characteristics. Likewise, for the paired kidney analysis, differences were evaluated by Student's paired t-test or the Wilcoxon signed rank test. Moreover, association of variables was evaluated by contingency tables with corresponding significance test (chi-square, Fisher's exact) and (multiple) linear regression analysis. The distribution of time to graft failure (deaths censored) was estimated by the Kaplan–Meier method and compared between the groups by the log-rank test. P values smaller than 0.05 were considered to indicate statistical significance. Statistical analysis was performed using the software SPSS Statistics 24 (IBM Corp., Armonk, NY, USA).

Results

During the study period, 941 kidney transplantations were performed including 113 transplantations procedures after allocation by RA or REAL (12%). 58 transplantations were performed, where both kidneys from the same donor were allocated to the same transplantation center to two different recipients. The 1-year follow-up data were completed for 112 of 113 procedures (99%).

Four groups of the deviated allocation modes were compared as follows (Figure 1):

1. *Rescue Allocation old (RAold)* includes all procedures from December 1, 2012, until December 8, 2013, during this time frame, only rescue allocation was available.
2. *Rescue Allocation new (RAnew)* includes all RA procedures from December 9, 2013, until December 31, 2014, kidneys allocated via REAL (before RA in this time period) had been excluded.
3. *REAL* includes all procedures from December 9, 2013, until December 31, 2014, when kidney grafts were only allocated via REAL.
4. *RAnew + REAL*. This group represents the complete spectrum of rescue allocation procedures after

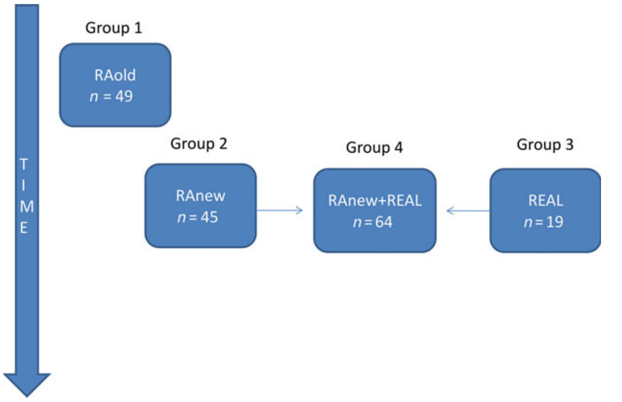

Figure 1 Groups of deviated allocation modes. Figure show the groups analyzed in this study. *RAold* includes all kidney transplantations after rescue allocation until December 8, 2013. At December 9, 2013, Eurotransplant introduced the REAL (recipient oriented extended allocation). From that time, rescue allocation (RAnew) was initiated, if no recipient could be found by REAL.

introduction of REAL in December 9th of 2013. This group, in terms of kidney allocation, is comparable to RAold.

Table 1 presents the donor characteristics. For this analysis, RAold was compared to RAnew, RAnew + REAL and REAL. Donor age was lower for RAold compared to RAnew and RAnew + REAL. There was a significant difference in donor weight comparing RAnew + REAL vs. RAold ($P = 0.037$) with significant less weight in RAnew compared to REAL (74.0 ± 20.2 kg vs. 93.2 ± 20.6 kg, $P = 0.01$). A significant difference was also seen in serum creatinine before procurement, which was less for RAnew vs. RAold (1.0 ± 0.5 mg/dl vs. 1.9 ± 1.3 mg/dl, $P = 0.001$) and for RAnew + REAL vs. RAold (1.2 ± 0.9 mg/dl vs. 1.9 ± 1.3 mg/dl, $P = 0.008$). Similarly, donor serum creatinine had a tendency to be higher in REAL than in RAnew (1.7 ± 1.3 mg/dl vs. 1.0 ± 0.5 mg/dl, $P = 0.052$). Diuresis during the last hour before procurement was significantly higher in the REAL group compared to RAold ($P = 0.017$). Likewise, REAL donors had a significantly longer stay on ICU before procurement compared to RAold and RAnew ($P = 0.001$). The number of refusals per kidney prior to acceptance and transplantation was higher for RAnew + REAL vs. RAold (12.1 ± 7.6 vs. 8.6 ± 8.6, $P = 0.004$) and also for REAL vs. RAold (12 ± 7.1 vs. 8.6 ± 8.6, $P = 0.036$).

There was no significant difference in age, weight, the rate of hypertension or diabetes mellitus or the number of mismatches. Table 2 shows the characteristics of the designated recipients before transplantation. However, median waiting time tended to be longer for REAL vs. RAnew (6.5 ± 3.0 years vs. 5.1 ± 2.6 years, $P = 0.065$). Allocation points were significantly lower comparing RAnew vs. RAold (481 ± 112 vs. 659 ± 259, $P < 0.0001$) and for RAnew vs. REAL (481 ± 112 vs.756 ± 94, $P < 0.0001$) and also for RAold vs. REAL (659 ± 259 vs 756 ± 93, $P = 0.022$).

Table 3 shows the results after transplantation including the follow-up data. There were no statistical differences in delayed graft function, surgical complication rate and rejection rate in all groups. 56% of the surgical complications in the overall cohort (N = 113) were classified as ≥Grade 3b according to the Clavien–Dindo classification [6]. In five cases, postoperative bleeding led to surgical revision; in three cases, vascular

Table 1. Characteristics of the donors allocated via REAL or RA.

	All	RAold	RAnew + REAL	RAnew	REAL
No.	113	49	64	45	19
Age (years)	55.6 ± 16.6	53.1 ± 18.1	57.5 ± 15.1 $P = 0.32$*	58.9 ± 16.3 $P = 0.08$*	54.4 ± 11.9 $P = 0.41$* $P = 0.03$†
Weight (kg)	82.3 ± 24.6	85.8 ± 27.6	79.7 ± 22.0 $P = 0.04$*	74.0 ± 20.2 $P = 0.002$*	93.2 ± 20.6 $P = 0.48$* $P = 0.001$†
Creatinine (mg/dl)‡	1.5 ± 1.2	1.9 ± 1.3	1.2 ± 0.9 $P = 0.01$*	1.0 ± 0.5 $P = 0.001$*	1.7 ± 1.3 $P = 0.65$* $P = 0.05$†
Diuresis last hour (ml)‡	163 ± 149	156 ± 160	167 ± 142 $P = 0.56$*	136 ± 103 $P = 0.71$*	240 ± 192 $P = 0.38$* $P = 0.02$†
Days on ICU‡	5.1 ± 8.6	3.9 ± 3.3	5.9 ± 10.9 $P = 0.53$*	4.9 ± 10.1 $P = 0.03$*	8.5 ± 2.4 $P = 0.017$* $P = 0.000$†
Refusals	10.5 ± 8.2	8.6 ± 8.6	12.1 ± 7.6 $P = 0.004$*	12.1 ± 7.8 $P = 0.01$*	12 ± 7.1 $P = 0.036$* $P = 0.76$†
Refusals (medical)	8.1 ± 7.4	6.7 ± 7.1	9.3 ± 7.5 $P = 0.045$*	9.6 ± 7.9 $P = 0.07$*	8.6 ± 6.7 $P = 0.16$* $P = 0.76$†

*Tested for significant difference to RAold, †tested for significant difference to RAnew, ‡before procurement.

Table 2. Characteristics of the recipients chosen for kidney transplantation after REAL or RA.

	All	RAold	RAnew + REAL	RAnew	REAL
No.	113	49	64	45	19
Age (years)	56.6 ± 13.8	55.4 ± 15.8	57.5 ± 2.1 P = 0.81*	57.3 ± 13.0 P = 0.80*	58 ± 10 P = 0.89* P = 0.73†
Weight (kg)	75.6 ± 20.1	72.6 ± 22.9	78.0 ± 17.3 P = 0.18*	78.3 ± 18.3 P = 0.21*	77.2 ± 15.5 P = 0.38* P = 0.73†
MaxcPRA0%	74%‡	74%	73% P = 0.99*	73% P = 0.99*	74% P = 0.99* P = 0.98†
DM	15%	12.2%	17.2% P = 0.33*	20% P = 0.18*	10.5% P = 0.84* P = 0.39†
Hypertension	91.2%	91.8%	90.6% P = 0.43*	88.9% P = 0.32*	94.7% P = 0.68* P = 0.63†
Waiting time (years)	5.6 ± 2.8	5.7 ± 2.9	5.5 ± 2.7 P = 0.59*	5.1 ± 2.6 P = 0.23*	6.5 ± 3.0 P = 0.36* P = 0.07†
Rank in Match	289 ± 491	256 ± 511	314 ± 479 P = 0.04*	411 ± 542 P = 0.01*	84 ± 65 P = 0.83* P = 0.004†
Allocation points	611 ± 215	659 ± 259	574 ± 168 P = 0.10*	481 ± 112 P = 0.000*	756 ± 94 P = 0.02* P = 0.000†

DM, diabetes mellitus; MaxcPRA0%, percentage of recipients with a maximum of 0% cPRA. *Tested for significant difference to RAold, †tested for significant difference to RAnew, ‡mean MaxcPRA%-level in the whole cohort (n = 113) was 3.7%, and one recipient had a MaxcPRA%-level of 100% with 0% cPRA at time of transplantation.

complications were seen at the renal vessels and three times the ureteral anastomosis was revised. During the 12-month follow-up, three recipients were subject to a laparoscopic deroofing of a lymphocele. Cold ischemia time (CIT) was significantly shorter for the REAL group (13.6 ± 3.6 h) compared to RAnew (17.2 ± 4.8 h, P = 0.019). CIT in REAL compared to RAold (16.1 ± 4.9 h, P = 0.067) was not statistically different. No statistical significant difference was seen for graft function at the end of the hospital stay (2.1–2.4 mg/dl). Serum creatinine levels after 1 year were comparable in all groups (1.6 ± 0.7 to 2.0 ± 1.1 mg/dl; P = 0.322). One-year graft survival rate was comparable with 87.8% for RAold vs. 85.9% for RAnew + REAL (P > 0.05).

Analysis in cases if both kidneys from the same donor were transplanted to two recipients in the same transplant center

From 29 donors, both kidneys were transplanted in the same center (58 transplantation procedures, 51% of the transplantations) to two recipients. Graft survival was shorter than 1 year in nine transplanted kidneys. "Never functioning" kidney grafts were observed after 11 transplantations, including four transplants from the same donor. In functioning paired grafts (38 grafts from 19 donors), there was a relevant difference in recipients' serum creatinine after 1 year comparing both kidneys (mean ± SD 0.61 ± 0.48 mg/dl, Fig. 2). These 19 pairs of kidney grafts were entered in a (multiple) linear regression analysis of "delta serum creatinine after 1 year" on "delta age (years)", "delta BMI (kg/m²) and "delta cold ischemia time (minutes)". There only delta age was significantly influencing graft function (P = 0.011) with a drop of 0.019 mg/dl per year, that is older recipients showed lower serum creatinine. The other analyzed factors (recipient BMI, CIT, hypertension, diabetes mellitus, %PRA and acute rejection) showed no significant influence on 1-year graft function in this group.

Figure 3 shows the rate of kidney transplantations performed after REAL/RA in the participating centers to the total performed kidney transplantations. Five

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Table 3. Results of kidney transplantation after REAL or RA.

	All	RAold	RAnew + REAL	RAnew	REAL
No.	113	49	64	45	19
CIT (h)	16.2 ± 4.8	16.1 ± 4.9	16.3 ± 4.8 *P* = 0.98*	17.2 ± 4.8 *P* = 0.34*	13.6 ± 3.6 *P* = 0.07* *P* = 0.02†
DGF	46	46.9	45.3 *P* = 0.68*	37.8% *P* = 0.42*	63.2% *P* = 0.23* *P* = 0.16†
Surgical complications	22.1%	22.4%	21.9% *P* = 0.64*	20% *P* = 0.44*	26.3% *P* = 0.94* *P* = 0.53†
Rejection	36.3%	34.7%	37.5% *P* = 0.89*	37.8% *P* = 0.90*	36.8% *P* = 0.93* *P* = 1.0†
Creatinine EOHS (mg/dl)	2.3 ± 1.2	2.4 ± 1.3	2.2 ± 1.12 *P* = 0.28*	2.2 ± 1.3 *P* = 0.32*	2.1 ± 0.8 *P* = 0.46* *P* = 0.80†
Creatinine 1 Year (mg/dl)	1.8 ± 0.8	1.8 ± 0.7	1.8 ± 0.9 *P* = 0.67*	1.6 ± 0.7 *P* = 0.41*	2.0 ± 1.1 *P* = 0.68* *P* = 0.32†
1-year graft survival‡	86.7%	87.8%	85.9%	86.7%	84.2%

CIT, cold ischemia time; DGF, delayed graft function; EOHS, end of hospital stay.*Tested for significant difference to RAold, †tested for significant difference to RAnew, ‡death-censored.

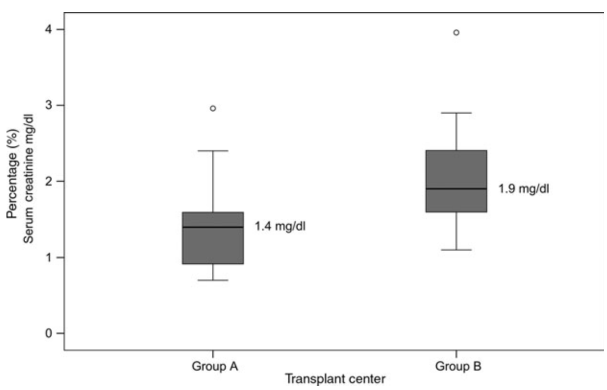

Figure 2 Difference in graft function, if two kidneys from one donor were transplanted to two recipients at one transplant center. Figure shows the graft function if two kidneys from one donor were transplanted to two recipients in one center (n = 19 pairs). These pairs of donor kidneys were divided into a group with the lower (Group A) and the higher serum creatinine (Group B). The difference between the groups was (mean ± SD) 0.61 ± 0.48 mg/dl. In a (multiple) linear regression analysis of "delta serum creatinine after 1 year" on "delta age (years)", "delta BMI (kg/m²") and "delta cold ischemia time (minutes)", only "delta age" was significantly influencing graft function (P = 0.011) with a drop of 0.019 mg/dl per year.

transplant centers had a higher transplantation rate compared to the five other centers. The transplantation rate ranged from 0% to 22% in the study period.

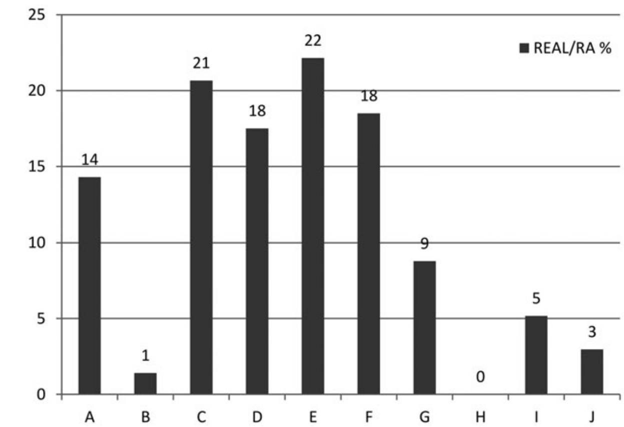

Figure 3 Percentage of performed kidney transplantations after REAL/RA in the study period of totally performed kidney transplantations in the participating centers. *X-axis* transplant center (anonymized), *y-axis* percentage of transplantations performed after REAL/RA (%).

Discussion

Kidney grafts not accepted by SAP represent a heterogeneous group of organs. In many cases, these kidneys are not accepted due to medical reasons, but sometimes no obvious reasons can be found. Identifying an appropriate recipient for a kidney graft offered in a deviant allocation scheme is a challenge for the transplant physician on call. In the former RA era, where any recipient from the center waiting list could be chosen, a balance between reduced waiting time and conversely potentially lower graft quality has been an acceptable decision. As ET changed the allocation system, new criteria for recipient selection have to be defined and have to be evaluated for their benefit.

The main finding of our study is that REAL influences recipient selection and that graft outcome after REAL/RA is influenced by the age of the recipient. Patients that were transplanted after the introduction of REAL needed more allocation points to receive an organ and had longer waiting times compared to recipients in the former RA era. Importantly, also the number of previous refusals per organ was significantly higher in the REAL era, likewise the stay on ICU was longer prior to donation. At the same time the outcome compared to the RA era did not change: The DGF rate is high with 45% (REAL group 63%), rejection rate was 36%, and 1-year graft survival of 85% was acceptable for these marginal kidney grafts. Although 1-year graft survival and graft function were comparable between the groups, the DGF rate in the REAL group was the highest (63%). An explanation for this finding could be a poorer donor quality, represented, for example, by the highest donor weight of all groups (average 93 kg) and the longest stay on the ICU prior to donation (average 8.5 days). One can speculate that the combination of a higher serum creatinine compared to the RAnew group (1.7 mg/dl vs. 1.0 mg/dl) and the high diuresis rate in this group (240 ml in the last hour prior to donation) could be already hinting to the development of a polyuric acute kidney failure in kidneys grafts in the REAL group, which fostered the appearance of DGF after transplantation. The diagnosed acute rejections were in the majority of the cases t-cell mediated. Biopsy-proven antibody-mediated rejections were detected in 12% only. This rate seems reasonable due to the low rate of retransplantations (6%) and highly immunized recipients (1%) in this cohort. Rather, ischemia/reperfusion injury (IRI) might have a strong negative impact on these marginal grafts. IRI and DGF could be a trigger for acute (cellular) rejections [7].

In general, graft survival at all seems to have slightly improved compared to the previous results of RA [3]. The majority of kidney grafts allocated via REAL/RA are expanded criteria donor (ECD) kidneys following OPTN/UNOS definition [8]. A recent meta-analysis by Querard *et al.* analyzing graft function for ECD kidney grafts showed a 1-year graft survival of comparable to the results of the REAL/RA kidney grafts [9]. A difference to other ECD grafts seems to be the rate of primary nonfunction after REAL/RA.

An increase in waiting time and in allocation points was expected as a consequence of the REAL system, as potential recipients with a higher ranking on the primary matching list in the standard allocation procedure have a better chance to receive an allograft offer, given that they were chosen by the transplant physician. This was approved by the data of this study.

Remaining on the waiting list or accepting a marginal yet viable graft is an individual decision, considering the fact that waiting time *per se* is a strong risk factors regarding the outcome after kidney transplantation [10]. In particular, in this setting, a reasonable communication between physician and patient is necessary for an informed, joined decision. Recent US data showed even a mortality benefit for patients receiving a marginal organ, which was allocated by nonstandard allocation, compared to those patients who remain on the waiting list. REAL/RA kidney grafts seem to provide a comparable benefit. Interestingly, simple labeling of marginal organs with a high kidney donor profile index leads to higher discard rates ("labeling effect") [11]. REAL/RA also labels and downgrades the kidney grafts—and 12 refusals before transplantation do reflect this. This downgrading of acceptable organs followed by refusals was described also as the "cascade effect" [3,12,13].

Since the introduction of REAL, the discard rates in the ET region have been kept low at about 8%, which is comparable to the RA era before [5]. This is remarkably taking the growing percentage of organs into account that were allocated at present by nonstandard allocation in ET area—and compared to US data, showing discard rates of 18% [11].

A topic deserving further investigation is the influence of recipient age on graft function after REAL/RA. Comparing kidney pairs of the same donor the older recipients seem to have higher benefit from REAL/RA with lower serum creatinine compared to the younger ones. These data could help to improve the individual risk-benefit assessment and finally to identify a suitable recipient for a REAL/RA kidney grafts. In this study, a difference in the transplantation rates after REAL/RA between the centers was seen, which could be an indication for different center policy for the acceptance of these special grafts.

One aim and benefit of REAL was to increase transparency during the allocation process: Organ allocation was preceded by a match list provided by ET; every step of this decision process is documented and could be reviewed afterward. Interesting and demanding is the high rate of organs that went from REAL to RAnew or were directly allocated via RA.

The evidence in the literature for primarily declined but afterward transplanted kidney grafts is scarce. This study provides the first analysis of the ET REAL system comparing the outcomes of 113 transplanted marginal organs. It sheds some light on recipient selection and graft outcome. Nevertheless, a limitation of the study is the relatively small number of transplantations performed after REAL. As REAL was newly introduced, transplant physician was not accustomed to the new allocation mode and to its online-based characteristic. This could produce a potential bias. Future studies on a broader database would be necessary to strengthen evidence about allocation and outcomes of this special subgroup of viable kidney grafts.

In conclusion, the REAL requires selection of recipients with significant more allocation points compared to the former RA era for successful organ receipt. Nevertheless, graft function was comparable in both time periods. Furthermore, recipient age seems to influence graft outcome. It is advisable to perform a thorough individual risk-benefit assessment during every REAL/RA procedure.

Authorship

RW: designed study, performed study, collected data, analyzed data, wrote the paper and coordinated the study. BS: designed study, performed study, collected data and wrote the article. WA, UE, TF, KI, TK, CK, AM, MN, SR and RW: performed study, collected data and wrote the article. FC, AH, UL, KS and RV: performed study and collected data. AK: performed study and wrote the article. MH: performed statistical consulting, analyzed data, wrote the article and reviewed the article. DLS: designed study, performed study, wrote the article and reviewed the article.

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Conflict of interest

The authors declare no conflict of interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. eCRF.

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