ORIGINAL ARTICLE

The 6-year clinical outcomes for patients registered in a multiregional United States Kidney Paired Donation program - a retrospective study

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SUMMARY

We examined what happened during a 6-year period to 1121 end-stage renal disease patients who registered with their willing/incompatible living donors for kidney exchanges with the Alliance for Paired Donation (APD). Of all patients, 65% were transplanted: 37% in kidney paired donation (APD-KPD, APD-other-KPD); 10% with compatible live donors (APD-LD); and 18% with deceased donors (APD-DD). The remaining patients were withdrawn (sick/died/others; 15%), or were still waiting (20%). For those patients with a cPRA 0–94%, 72% received a transplant. In contrast, only 49% of very highly sensitized (VHS; cPRA 95–100%) were transplanted. Of the VHS patients, 50% were transplanted by KPD/APD-LD while 50% benefited through prioritization of deceased donors in the modified kidney allocation system (KAS introduced in 2014). All APD transplanted groups had similar death-censored 4-year graft survivals as their relevant Organ Procurement and Transplantation Network (OPTN) groups. It is noteworthy that VHS graft and patient survival results were comparable to less sensitized and nonsensitized patients. All patients should be encouraged to search for compatible donors through different options. Expanding the donor pool through KPD and the new KAS of the OPTN increases the likelihood of transplantation for VHS patients.

Introduction

While renal transplantation remains the gold-standard for patients with end-stage renal disease (ESRD), the greatest obstacle is the limited availability of organs. The Organ Procurement and Transplantation Network (OPTN) waiting list of more than 100 000 patients continues to grow, as only about 12 000 deceased donor (DD) and almost 6000 living donor (LD) transplants are performed every year [1,2]. Multiple reports have indicated benefits to receiving a LD transplant such as less delayed graft function (DGF) and better long-term kidney allograft survival [3–8]. Indeed, LDs not only offer higher quality kidney transplants than DDs, they often constitute better donor/recipient matching [1,9–12]. For example, OPTN reported 1-year and 5-year LD kidney allograft survival rates of 96% and 81%, respectively, versus 91% and 69% for DDs [1].

Over the last decade, an effort has been made to increase living donation through kidney paired donation (KPD). Although KPD arranged only six exchanges in 2002, there were 450 exchanges in 2010, 587 in 2015 and 642 in 2016 [1]. The rapid growth of organized kidney exchanges was motivated by early successes [13–23], including the Ohio Solid Organ Transplantation Consortium and the Alliance for Paired Donation (APD), together active since 2001. Now, the APD, consisting of over 80 transplant programs in 30 states, utilizes 2-, 3- and multiple-way simultaneous exchanges (cycles) and nonsimultaneous exchanges [24]. Recently published APD results demonstrated that 22% of offers were accepted and 16% of offers resulted in transplants [25]. The same analysis revealed that chains were 2.5 times more successful than cycles in producing transplants, as even incomplete chains always led to at least one transplant [25]. In contrast, when any offer within a cycle was rejected it resulted in cancellation of all planned pairs.

However, it is not clear what may be the best advice for patients who register on a KPD waiting list. To review different options, we examined clinical outcomes of all patients registered in APD with the collaboration of the United Network for Organ Sharing (UNOS)/OPTN. UNOS linked the list of APD-registered patients between January 2010 and January 2016 to two different OPTN databases. Overall, this report represents an evaluation of options for and outcomes of 1121 patients who registered with the APD. For those who received kidney transplants, graft outcome was analysed with respect to transplantation method (KPD, LD, or DD) and level of sensitization. We also analysed how DD groups benefited through two special OPTN programs, namely zero mismatch (0MM) and the new kidney allocation system (KAS) in finding matching donors for very highly sensitized (VHS; cPRA 98–100%) patients.

Materials and methods

Patient cohorts

The UNOS-linked APD-registered patients to the OPTN database provided clinical outcomes along with demographics compared to national results (IRB approved, #104347). Four patient cohorts were analysed: (i) APD-registered patients (between January 2010 and January 2016) matched to the OPTN waiting list ($n = 1121$). These data were stratified by cPRA provided by the transplant center; (ii) APD-registered patients in the first cohort who received a LD or DD kidney transplant

between January 2010 and January 2016 ($n = 712$) matched to the OPTN database; (iii) APD-active cohort consisted of patients participating in the APD match-run in February of 2016 ($n = 129$); and (iv) APD-KPD transplanted patients between January 2010 and August 2016 ($n = 182$). For comparison, UNOS provided data for patients who received a kidney transplant in the U.S. between January 2010 and January 2016. This population was stratified in a similar manner to the APD patient.

The APD data were stratified by the recipient's level of sensitization at transplantation (cPRA 0-19%, 20–79%, 80–100%, 95–100%) for APD-registered, APD-active, or APD transplanted groups. The OPTN data included: (i) sensitization level at the time of removal from the waiting list; and (ii) up-to-date analysis of clinical outcomes for patients receiving a DD or LD transplant.

For 712 APD-registered/transplanted patients were analysed in the following groups: APD-registered and transplanted with an APD-arranged KPD transplant (APD-KPD); APD-registered but transplanted through collaboration between APD and other KPD programs (APD-other-KPD); all patients transplanted *via* KPD (OPTN-KPD); patients transplanted with a compatible LD registered either with APD (APD-LD) or OPTN (OPTN-LD); and patients transplanted with a DD registered either with APD (APD-DD) or OPTN (OPTN-DD). Additionally, we calculated time on the APD waiting list using APD registration dates for patients stratified by sensitization and blood groups.

Algorithm used by the APD program

The APD-matching software describes a "pair" as a recipient with a willing-but-incompatible donor versus a "combination" as a recipient with a willing compatible donor from a different pair. Out of 85 transplant centers in the US affiliated with APD 77 entered at least one pair into the APD registry between January 2010 and January 2016. A typical pool of ≈150 pairs has ≈22 000 conceivable *combinations*: the "algorithm" eliminates unusable *combinations* proposing cycles and chains. First, the "summary exclusion criteria" eliminates *combinations* of ABO and HLA (based on unacceptable HLAs for sensitized patients) incompatibility. Secondly, the "discretionary exclusion criteria" eliminates *combinations* based on indicated preferences: for example, age of donor, BMI, hypertensive medication use by the donor, etc. Since 86% of *combinations* are eliminated, ≈3000 feasible *combinations* undergo the

APD scoring system (Table S1). The final cycles and chains are identified by an "optimization algorithm" designed by Utku Unver, Tayfun Sonmez and Alvin Roth [26–28]. The optimization finds cycles and chains producing the highest number of transplants weighted by quality as defined by the APD scoring system. Match runs were performed daily for the presented data [29].

Statistical analyses

United Network for Organ Sharing analysed up-to-date graft survival rates and Kaplan–Meier death-censored graft survival rates. The rate of transplantation was evaluated using Student's t test or the Kruskal–Wallis test. DGF, CIT and acute rejection for APD patients were compared to overall data reported to the OPTN for transplanted patients. Analyses were performed by Chi-squared tests with Bonferroni corrections for multiple variables. The Pearson's Chi-square test was used to examine the impact of cPRA levels on the chance to receive kidney transplants. The 2-way ANOVA with interaction was used to examine the relation of cPRA levels in patients with A versus O blood groups on their waiting time. In all performed analyses P-values <0.05 were considered as statistically significant.

Results

Characteristics of all patients registered in the APD

Characteristics of all 1121 APD-registered candidates are described in Table 1 whereas of 712 APD-registered transplanted patients in Table 2. In addition, Table 2 presents characteristics of transplanted patients in US for the same time period. Overall, there was a similar distribution of gender, ethnicity and original diagnosis across the differently transplanted groups in APD and OPTN, with very few exceptions (Table 2).

Overall outcomes among all APD-registered patients

As the OPTN waiting list analysis showed, between January 2010 and January 2016, 727 out of 1121 APD-registered patients (65%) were transplanted through the following options: 224 patients (20%) were transplanted through APD-KPD and 188 patients (17%) by APD-other-KPD (37% total through kidney exchanges), 111 patients (10%) received transplants from compatible LDs, and 204 patients (18%) from DDs (Table 3). The remaining 224 (20%) were still waiting, 110 (10%) were withdrawn from the list because of death or sickness,

Table 1. Characteristics of APD-registered patients.

Characteristics of the patients	N	%	Characteristics of the patients	N	%
Sex %			Dialysis		
Female	558	49.8	No	371	33.1
Male	563	50.2	Yes	750	66.9
Race/Ethnicity			Prior kidney tx		
White	798	71.2	No	739	65.9
Black	160	14.3	Yes	382	34.1
Hispanic	107	9.5	ABO		
Asian	43	3.8	A	254	22.7
Amer Ind/Alaska Native	8	0.7	A1	3	0.3
Native Hawaiian/other Pacific Islander	1	0.1	A2	1	0.1
Multiracial	4	0.4	AB	23	2.1
Diagnosis			B	166	14.8
Glomerular Diseases	315	28.1	O	674	60.1
Diabetes	190	16.9	PRA		
Retransplant/Graft Failure	154	13.7	0–19%	463	41.3
Polycystic Kidneys	134	12	20–79%	202	18.0
Hypertensive Nephrosclerosis	129	11.5	80–94%	119	10.6
Other	111	9.9	95–100%	337	30.1
Tubular and Interstitial Diseases	44	3.9			
Congenital, Rare Familial and Metabolic Diseases	25	2.2	APD-registered total	1121	100
Renovascular and Other Vascular Diseases	15	1.3			
Neoplasms	4	0.4			

UNOS analysis of OPTN waiting list data; Registrations are between January 2010 and January 2016.

Table 2. Characteristics of transplanted patients stratified by transplantation group.

Characteristics of the patients	APD-KPD N = 223	APD other KPD N = 186	APD-LD N = 110	APD-DD N = 193	OPTN all KPD N = 2946	OPTN-LD N = 31 512	OPTN-DD N = 68 363
Mean Age (years)	52	50.6	47.3	48.1	48.4	46.6	51.4
Sex %							
Female	51.6	48.9	45.5	49.7	44.6	36.9	39.6
Male	48.4	51.1	54.5	50.3	55.4	63.1	60.4
Ethnicity %							
White	70.9	75.3	79.1	72	62.6	66.5	42.3
Black	14.3	12.9	8.2	12.4	15.9	12.8	**32.5**
Asian	4	5.9	4.5	1.6	6.2	4.7	6.6
Hispanic	9.9	5.9	7.3	13.5	14	14.6	16.7
Other	0.9	0	0.9	0.5	1.3	1.4	1.9
Diagnosis %							
Diabetes	18.8	17.2	15.5	10.4	20.6	21	26.1
Hypertension	16.6	13.4	10.9	12.4	15.4	15.3	22.5
Glomerulonephritis	25.6	24.7	30.9	34.2	25.2	28.4	19.9
Cystic Disease	13.9	12.9	17.3	10.4	12.4	11.5	7.4
Other	4%	4.8	8.2	5.7	4.9	6.3	6.2
Dialysis %							
Pre-emptive tx	22.4	21	22.7	14.5	28.5	36.9	13.7
Dialysis < 1 year	18.4	16.7	27.3	7.3	21	27	10.3
Dialysis < 3 years	49.8	51.1	58.2	31.1	49.1	52.3	33.1
Dialysis < 5 years	68.2	67.7	70	58	62	59.3	55.8
Dialysis > 5 years	9.4	11.3	7.3	**27.5**	9.5	3.9	**30.4**
Mean dialysis time	2.8	2.9	2.3	**4.3**	2.7	1.8	**4.4**
Re-transplant %	13.5	16.7	10.9	17.6	13.6	5.6	7
Blood group %							
Blood group A	32.3	26.3	22.7	17.6	36.5	39.3	35.8
Blood group B	17.9	16.1	13.6	10.9	17.8	13	13.1
Blood group AB	2.7	2.2	1.8	2.1	6	3.9	5.4
Blood group O	47.1	55.4	61.8	69.4	39.8	43.8	45.6
HLA Mismatches %							
HLA MM 0	2.7	1.6	4.5	**20.2**	0.7	7.5	6.9
HLA MM 1	1.3	3.2	3.6	1	1.5	4.9	1
HLA MM 2	6.7	4.8	13.6	8.8	5.5	15.6	4.3
HLA MM 3	13.5	14	18.2	18.1	15.3	26.3	13.3
HLA MM 4	26	23.1	23.6	24.9	26.1	15.5	26.8
HLA MM 5	29.6	32.3	25.5	18.7	32.3	18.9	31.5
HLA MM 6	17	18.8	10.9	8.3	16.7	10.5	15.4

Table 2. Continued.

Characteristics of the patients	APD-KPD N = 223	APD other KPD N = 186	APD-LD N = 110	APD-DD N = 193	OPTN all KPD N = 2946	OPTN-LD N = 31 512	OPTN-DD N = 68 363
HLA MM missing	3.1	2.2	0	0	1.8	0.7	0.7
cPRA at transplant %							
0–19	52	40	56	33	60	78	69
20–79	24	23	15	15	21	11	15
80–94	11	10	11	16	9	2	9
95–100	11	25	14	**36**	7	1	7
cPRA missing	2	2	4	0	3	8	0
Mean CIT (hours)	6.9	6.6	1.9	17.3	4.8	1.9	17.1
Delayed Graft Function %	3.1	3.8	5.5	18.7	4.4	3	25.6
Total number	223	186	110	193	2946	31 512	68 363

UNOS analysis of OPTN transplants data; transplants occurred between January 2010 and January 2016.

APD, Alliance for Paired Donation; CIT, cold ischaemia time; cPRA, calculated panel reactive antibodies; DD, deceased donor; KPD, Kidney Paired Donation; LD, living donor.

Bold numbers show significant values.

and 60 (5%) for unknown reasons (Table 3). Thus, the majority of APD-registered patients were transplanted during the 6-year period by exploring different possibilities.

Impact of sensitization on receiving transplants among APD-registered patients

Sensitization patterns in different groups were very revealing about the patient's likelihood of obtaining a kidney transplant (Fig. 1). Overall, 59% of all APD-registered patients had cPRA between 0% and 79%, while 41% had a cPRA between 80% and 100%, of whom 75% were very highly sensitized (VHS) with a cPRA of 95–100% (Table 1; Fig. 1). When all patients were divided into transplanted versus not-transplanted, they showed an interesting pattern (Fig. 2). Three cPRA groups up to 94% had consistently more transplanted than nontransplanted patients presented as numbers of patients (Fig. 2a) or as percentages in each group, namely: 71% of nonsensitized (NonS; cPRA = 0–19%), 73% of moderately sensitized (MS; cPRA = 20–79%) as well as 74% of highly sensitized (HS; cPRA 80–94%) patients found a matching transplant (Fig. 2b). This contrasted with VHS patients (cPRA 95–100%) wherein less than half of patients (Fig. 2a) or only 48% (Fig. 2b) of patients were transplanted. The impact of cPRA levels on the transplanted/nontransplanted status was statistically significant as confirmed by the Pearson's Chi-square analysis ($P < 0.0001$).

Even more insights were revealed when cPRA sensitization levels were examined for different groups: those transplanted with live donors (APD-KPD, APD-other-KPD and APD-LD) found matching donors more effectively for NonS/MS/HS patients than for VHS patients when calculated as numbers of transplants (Fig. 2c) or as percentages of transplanted versus nontransplanted in each cPRA group (Fig. 2d). In fact, these three live donor programs together transplanted 436 patients with a cPRA 0–94%, which was 77% of all APD-registered patients with cPRA 0–94%. The same three programs transplanted 87 patients with cPRA 95–100% or only 25% of those APD-registered with cPRA 95–100%. APD-DD alone found matches for 59 patients or only 16% of those with cPRA 0–94% and for 79 patients or 23% with cPRA of 95–100% (Table 3; Fig. 2d). Thus, a relatively small pool of live donors effectively supported patients with cPRA up to 94% but not those with cPRA equal to and above 95%. In contrast, access to DD donors expanded access to matches for VHS patients through the 0MM and new KAS special programs (see a

Table 3. OPTN waiting list outcomes for APD-registered patients.

PRA % APD groups	0–19		20–79		80–94		95–100		All
	n	%	*N*	%	*n*	%	*n*	%	*n* (% registered)
APD-KPD	121	54	56	25	22	9.8	25	11.2	224 (**20.0**)
APD-other-KPD	76	40.4	44	23.4	21	11	47	25	188 (**16.8**)
APD-LD	66	59.5	16	14.4	14	12.6	15	13.5	111 (**9.9**)
APD-DD	66	32.4	31	15.2	31	15	76	37.3	204 (**18.2**)
Waiting	78	33.1	33	14	16	7	97	41.1	224 (**20.0**)
Died/Sick	35	31.8	15	13.6	9	8	51	46.4	110 (**9.8**)
Other	21	35	7	11.7	6	10	26	43.3	60 (**5.3**)
All	463	41.3	202	18	119	10.6	337	30.1	1121 (**100.0**)

UNOS analysis of OPTN data, performed on November 18 2016; registrations occurred between January 2010 and January 2016.

APD, Alliance for Paired Donation; cPRA, calculated panel reactive antibodies; DD, deceased donor; KPD, Kidney Paired Donation; LD, living donor.
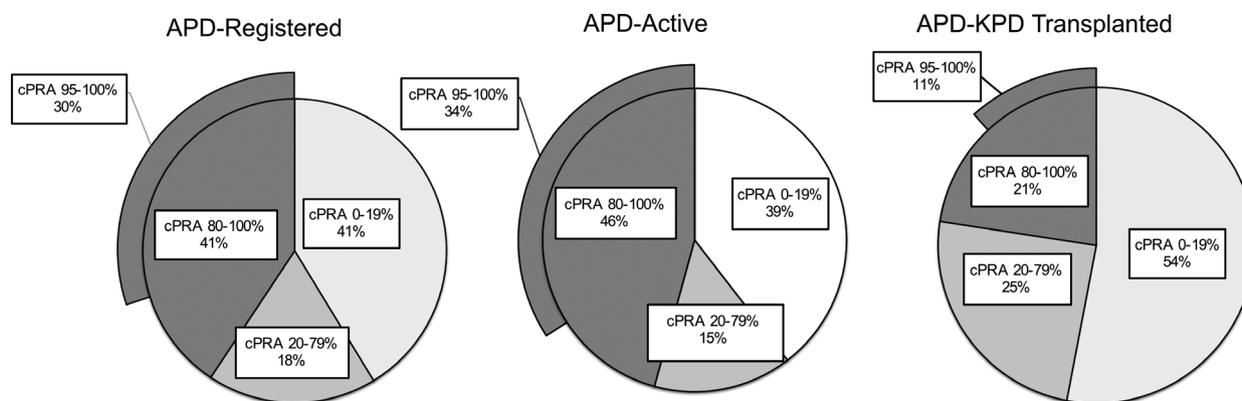

Figure 1 Sensitization patterns of patients in the APD program. Sensitization levels among 1121 patients who were registered in the APD program between January 2010 and January 2016 (APD-Registered, left), 129 patients who were on the active list and used for daily match run in February of 2016 (APD Active, center), and 224 patients who were transplanted in the APD-KPD program (APD-KPD Transplanted, right). Sensitization levels are stratified as follows: not sensitized (cPRA 0–19%), moderately sensitized (cPRA 20–79%) and highly sensitized (cPRA 80–100%), with a subset indicating very highly (cPRA 95–100%) sensitized.

section below about APD-DD patients). The Pearson's Chi-square analysis confirmed a statistically significant dependence of cPRA levels and the possibility for finding matches in each group (*P* < 0.0001) except of the APD-other-KPD program.

Clinical outcomes for the APD-KPD/APD-other-KPD patients

Clinical outcomes

Of 1121 APD-registered candidates, 409 were transplanted through the kidney exchange (APD-KPD/APD-other-KPD). Overall, their 6-year up-to-date graft survival was 95% in APD-KPD (Table 4). NonS

represented 51%, MS 24% and HS 22% of transplanted patients with 95-98% graft survival. Only 11% represented VHS patients but their graft survival was 96% (Table 4). These results were similar to relevant OPTN groups (Tables 4 and 5). The death-censored Kaplan–Meier 4-year graft survival for the APD-KPD patients (92.1%) was similar to APD-other-KPD (83.9%) and all OPTN-KPD-reported patients (88.0%; Fig. 3a), as shown by similar survival rates and overlapping confidence intervals (Fig. 3d).

APD-KPD performance

The APD-KPD made 419 formal offers with 1155 proposed transplants: only 103 offers were formally
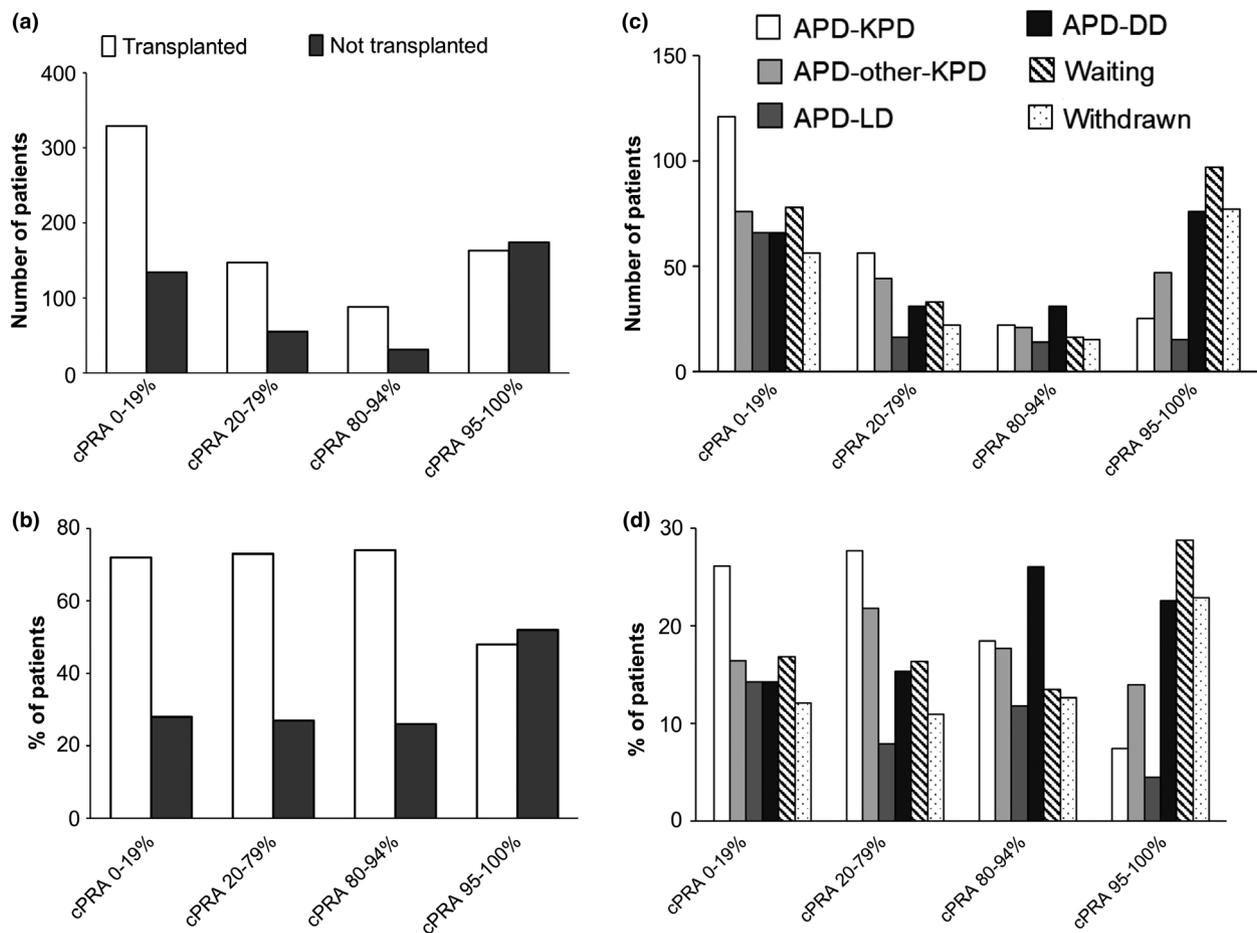
Figure 2 The impact of sensitization on receiving a transplant among APD-registered patients. All 1121 APD-registered patients were divided into 727 transplanted (in any APD group) versus 394 nontransplanted (still waiting/dead/sick/other) divided into the sensitization groups cPRA 0–19, 20–79%, 80–100% and 95–100% and shown as numbers of patients (a) or per cent of patients (b); and, All 1121 APD-registered patients were divided into APD-KPD, APD-other-KPD, APD-LD, APD-DD, still waiting and withdrawn (dead/sick/other) which were then each divided into the cPRA sensitization groups (0–19%, 20–79%, 80–94% and 95–100%) and presented as the actual number of patients in each group (c) or percentage of patients in each group (d). The Pearson's Chi-square test was used to examine the impact of cPRA levels on chances to receive kidney transplants.

accepted (25% success rate) producing 224 completed transplants (19% success rate; Fig. 4a). Since 77 transplants were accomplished through 2-, 3-, 4- and 6-way simultaneous cycles (Fig. 4b) whereas 147 transplants through nonsimultaneous 1-, 2-, 3-, 4-, 5-, 6- and 7-chains (Fig. 4c), chains were two times more successful than cycles. Every year except for 2014 chains were preferentially selected most likely because chains used 28 nondirected donors (NDDs) and 25 bridge donors (BDs). Indeed, lack of NDDs and matches for BDs in 2014 reduced the number of chain transplants to five transplants (one 3-way chain and two 1-way chains), with the remaining 31 transplants achieved through 2-, 3- and 4-way cycles (Fig. 4b). Every other year chains produced more transplants than cycles: that is, 9.5 times more in 2010 or 1.8 times more in 2015 (Fig. 4b and

c). These results show the flexibility between cycle and chain choices in the APD computer program.

From 2006 to 2009, donors in APD-KPD program travelled to the city of their recipients minimizing the cold ischaemia time (CIT) of transplants to 2 h. In 2010 the APD began shipping kidneys with an average 7-h CIT (Figure S1A). Despite this change APD-KPD patients had only 3% of transplants with delayed graft function (DGF), which was similar to 4% in OPTN-KPD and to 4.5% in OPTN-LD (Figure S1B). Additional review of donor's age in APD-KPD showed that despite 7-h CIT grafts from 50- to 64-year-old donors had similar 3-year graft survival as from young 18–35 year-old donors, which was confirmed by a parallel analysis of APD-LD, OPTN-KPD and OPTN-LD (Figure S2A-E). Thus, we found no disadvantage in the use of older donors for the KPD program.

Table 4. The up-to-date clinical outcomes for APD-registered patients.

Group of patients	n	cPRA%	Functioning graft %	Death with functioning graft %	Return on dialysis %
APD-KPD	115	0–19	94.8	2.6	1.7
	53	20–79	98.1	1.9	0
	24	80–94	92	4.2	4.2
	25	95–100	96	4	0
	6	cPRA missing	83.3	16.7	0
Total	223	All	95.1	3.1	1.3
APD-other-KPD	75	0–19	92	1.3	4
	42	20–79	95.2	2.4	0
	19	80–94	84.2	5.2	10.5
	47	95–100	95.7	0	2.1
	3	cPRA missing	66.7	0	33.3
Total	186	All	92.5	1.6	3.8
APD-LD	62	0–19	88.7	4.8	3.2
	17	20–79	100	0	0
	12	80–94	100	0	0
	15	95–100	93.3	0	6.7
	4	cPRA missing	75	0	25
Total	110	All	91.8	2.7	3.6
APD-DD	63	0–19	74.6	1.6	15.9
	29	20–79	86.2	3.4	6.9
	32	80–94	87.5	0	12.5
	69	95–100	84.1	4.3	8.7
Total	193	All	81.9	2.6	11.4
Total APD	712	All	90.3	2.5	5.1

UNOS analysis of OPTN transplants data, performed on May 27 2016; transplants occurred between January 2010 and January 2016.

APD, Alliance for Paired Donation; cPRA, calculated panel reactive antibodies; DD, deceased donor; KPD, Kidney Paired Donation; LD, living donor.

Clinical outcomes for the APD-LD patients

During a 6-year observation period 110 patients (10%) registered in APD found and received transplants from compatible LDs (Table 2). The death-censored 4-year survival of APD-LD kidney transplants of 90.2% was similar to overall 89.5% among OPTN-LD (Fig. 3b and d). As of May 2016, the up-to-date 6-year graft survival rate in the APD-LD program was 95% also matching OPTN-LD results of 95% (Tables 4 and 5). The APD-LD and OPTN-LD programs had similar 2-h CIT (Figure S1A) and very little DGF (Figure S1B).

Clinical outcomes for the APD-DD patients

APD-DD clinical outcomes

During the 6-year observation period 193 patients (18%) registered in APD obtained transplants from DDs (Table 2). The death-censored 4-year survival of

kidney transplants from DDs was 74.5%, which was similar to 80.3% observed in OPTN-DD patients (Fig. 3c and d). The up-to-date 6-year graft survival rate for APD-DD was 82% and that was also similar to 85% in OPTN-DD (Tables 4 and 5). The overall worse DD kidney allograft survivals in comparison to LD groups (Fig. 3a and b) correlated with a 16-h CIT (Figure S1A) and an 18% DGF (Figure S1B) in APD-DD. Similar 16-h CIT and 26% DGF were observed in OPTN-DD patients (Figure S1A and B).

Impact of OPTN programs on clinical outcomes

Because the APD-DD group contained many HS/VHS recipients (Fig. 1), we evaluated the impact of the 0MM and KAS on APD-DD transplants. By definition, the 0MM program benefited patients with HLA-A/-B/-DR matched donors with a cPRA > 20%, while after November 2014 the new KAS program specifically targeted patients with a cPRA ≥ 98% and those

Table 5. The up-to-date clinical outcomes for all patients

Group of patients	n	cPRA%	Functioning graft %	Death with functioning graft %	Return on dialysis %
OPTN-KPD	1791	0–19	91.4	3	3.6
	617	20–79	91.6	3.2	4.2
	242	80–94	90	2.5	4.5
	220	95–100	92.3	1.8	4.5
	76	cPRA missing	93.4	2.6	3.9
Total	2946	All	91.4	2.9	3.9
OPTN-LD	24541	0–19	92.4	3	2.6
	3449	20–79	92	3.3	2.7
	582	80–94	92.4	2.6	2.7
	427	95–100	87.4	3.7	5.4
	2513	cPRA missing	87.4	5.4	4.4
Total	31 512	All	91.9	3.3	2.8
OPTN-DD	47167	0–19	84.5	6.7	4.7
	10177	20–79	85.7	5.9	4.6
	5971	80–94	84.9	5.7	5.6
	5048	95–100	87.5	4.3	4.7
Total	68 363	All	84.9	6.3	4.8
Total	102 821	All	87.3	5.3	4.1

UNOS analysis of OPTN transplants data, performed on May 27 2016; transplants occurred between January 2010 and January 2016.

cPRA, calculated panel reactive antibodies; DD, deceased donor; KPD, Kidney Paired Donation; LD, living donor.
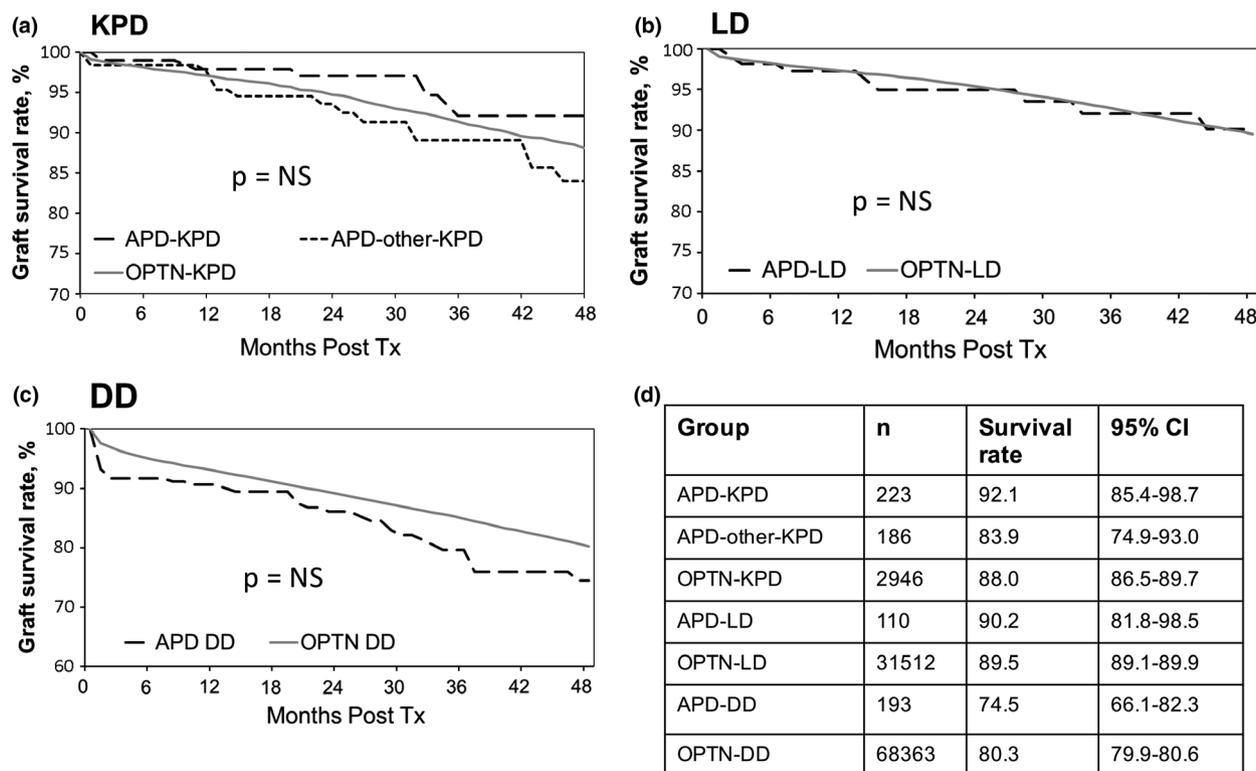
Figure 3 Kidney allograft survival in APD and OPTN groups. Kaplan–Meier death-censored 4-year graft survival of kidney allografts: (a) APD-KPD, APD-other-KPD, and overall all OPTN-KPD; (b) APD-LD and OPTN-LD for living donor recipients; (c) APD-DD and OPTN-DD for deceased donor recipients; and (d) Statistical analysis showing 95% confidence intervals (CI) for each group: there were no statistically significant differences among groups. All evaluated transplants took place between January 2010 and January 2016.

(a)

Success Rate	2010	2011	2012	2013	2014	2015	2016*	Total
Offers	60	59	43	80	90	78	9	419
1-Ways	210	171	100	211	242	196	25	1155
Successful Offers	9	20	18	17	15	22	2	103
Completed 1-ways	21	37	36	34	36	51	9	224
Offer SR	15.0%	33.9%	41.9%	21.3%	16.7%	28.2%	23.2%	24.3%
1-Way SR	10.0%	21.6%	36.0%	16.1%	14.9%	26.0%	18.9%	19.0%

*Transplants performed in January 2016
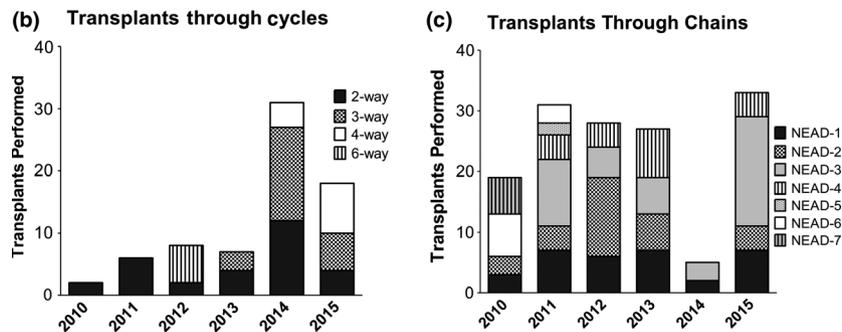
Figure 4 Analysis of cycles and chains in the APD-KPD program. (a) Success rate (SR) for offers was calculated by dividing number of proposed offers by successful (accepted) offers (Offer SR). Successful 1-way SR was calculated by dividing the number of 1-ways from proposed offers by the number of 1-ways from successful offers. (b) Cycles described kidney exchanges between noncompatible donor/recipient pairs which must be performed simultaneously by 2-, 3-, 4- or 6-way exchanges. In cycles both donor and recipient form each participating pair must be involved. (c) Chains or nonsimultaneous never ending donor chains (NEAD) are always initiated by nondirected (ND) donor (without attachment to any recipient on the list) or bridge donor (BD) donating a kidney to the first recipient in the chain. Consequently, donor from the first recipient become "free" to donate to any designated recipient: chain transplants are performed in a sequence. The last "freed" donor becomes a BD for a new chain. There are NEAD-1, -2, -3, -4, -5, -6 and -7 chains (number reflects performed transplants). Cycles (b) and chains (c) are divided into 2010 to 2015 years.

waiting $\geq$ 10 years on dialysis. Careful review of all 193 APD-DD recipients showed an interesting pattern (Fig. 5a). During the 6-year period, 39 patients (20.2%) were transplanted with 0MM donors (Table 2): 35 during 60 months prior KAS and four during 14 months after KAS. Analysis of the impact by the new KAS showed that 12 out of 43 VHS (28%) were transplanted prior KAS while 31 out of 43 VHS (72%) after KAS introduction. This observation clearly demonstrates the benefit for VHS patients (Fig. 5a). All these results confirmed that 69 APD-registered VHS patients benefited in APD-DD from either 0MM or the new KAS (Fig. 5a), representing 9.7% of all 712 transplants in APD-registered patients.

Organ Procurement and Transplantation Network patients for the same periods showed very similar trend prior to and after the new KAS introduction (Fig. 5b): 7.6% vs. 4.3% of DD transplants were 0MM prior to versus after December 2014, respectively. The new KAS elevated 5% of recipients who could benefit prior December 2014 to 15.5% of recipients who were transplanted after December 2014 (Fig. 5b).

Impact of sensitization and blood groups on the waiting time for transplants

We examined the waiting time between OPTN registration and transplantation with different sensitization levels (Fig. 6a). The shortest waiting time was for patients who found compatible LDs and/or who were mildly or nonsensitized (cPRA 0–79%): APD-LD patients waited 471 days and OPTN-LD patients 426 days. While HS patients had to wait longer in all groups, VHS recipients waited 1171 days in APD-DD and 1165 days in OPTN-DD groups (Fig. 6a).

Since blood groups significantly influenced the waiting time for transplants [30,31], we evaluated their impact in APD-KPD. We examined the waiting time between APD registration and transplantation. Nonsensitized patients with blood group A received grafts within 73 days, but required 335 days to transplant blood group O patients. The waiting time was extended to 314 days for HS and to 420 days for VHS patients with blood group A and to 502 days for HS and to 671 days for VHS with blood group O (Fig 6b). The
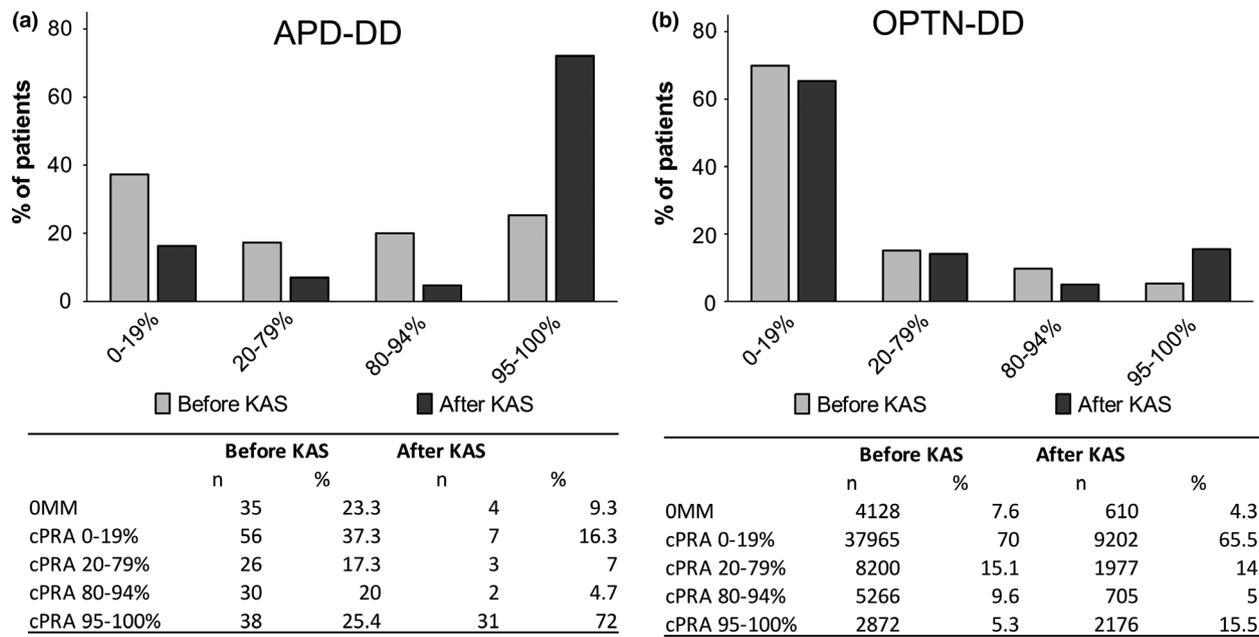
Figure 5 Impact of 0MM and KAS programs on transplants performed in APD-DD group and OPTN-DD groups. (a) All 193 APD-DD-transplanted recipients were divided into the sensitization groups and examined for time of their transplantation prior to (Before KAS) and after (After KAS) December 2014. Prior KAS represents APD-DD transplants performed between January 2010 and November 2014 whereas after KAS represents APD-DD transplants performed between December 2014 and January 2016. (b) All 142 229 OPTN-DD-transplanted recipients were divided into the sensitization groups and examined for time of their transplantation prior to (Prior-KAS) and after (After-KAS) December 2014. Prior-KAS represents OPTN-DD transplants performed between January 2010 and November 2014 whereas after-KAS represents OPTN-DD transplants performed between December 2014 and January 2016.

impact of blood groups and cPRA levels on waiting times were analysed by the 2-way ANOVA method with interaction showing a significant difference between waiting time and cPRA levels in blood group A versus blood group O ($P < 0.04$).

Discussion

Our main observation is that out of all APD-registered patients 65% received kidney transplants during a 6-year period by different options: kidney exchange (APD-KPD/APD-other-KPD; 37%), live compatible donor (APD-LD; 10%), or deceased donor (APD-DD; 18%). The remaining 35% were either still waiting (20%), were withdrawn because they were sick or died (10%), or for unknown reasons (5%). We propose that all KPD patients should be encouraged to pursue multiple strategies to achieve a kidney transplant rather than to remain on dialysis [8]. The death-censored graft survival results in all groups were excellent and comparable to the relevant OPTN groups (Fig. 3). Of particular interest is the fact that the good survival was true across all sensitization levels including VHS patients (Table 4).

The APD-KPD had very good survival results comparable to all OPTN-KPD-registered programs. The 4-year

Kaplan–Meier graft survival of 92% was similar to the overall 90% in OPTN (Fig. 3). Detailed analysis showed the flexibility between cycle and chain choices, which was dependent on the availability of NDDs and BDs. With the available NDDs/BDs chains were formed more easily than cycles and a sequential transplant possibility always accomplished at least one transplant. In contrast, one failed transplant in a cycle scrapped all planned transplants. Even with an average CIT of 7-h 50–64 year old donors produced good quality transplants comparable to 19–35 year old donors.

Overall worse results of APD-DD group, compared to KPD and LD groups, were likely related to the unique specifics, namely: (i) A large percentage of VHS (37.3%) patients; (ii) A large percentage (27.5%) of patients >5 years on dialysis; (iii) The longest average CIT (16 h); and, (iv) The high percentage of patients with DGF (18%). Sum of these negative factors likely worsened the graft survival rate in the APD-DD group. At the same time the APD-DD group provided benefits to hard-to-match patients. Since 37.3% of APD-DD recipients were VHS, we examined the impact of the new KAS introduction (November 2014; Fig. 5). During 6 year period, 39 patients received 0MM kidney transplants, 35 prior and four after the new KAS. After
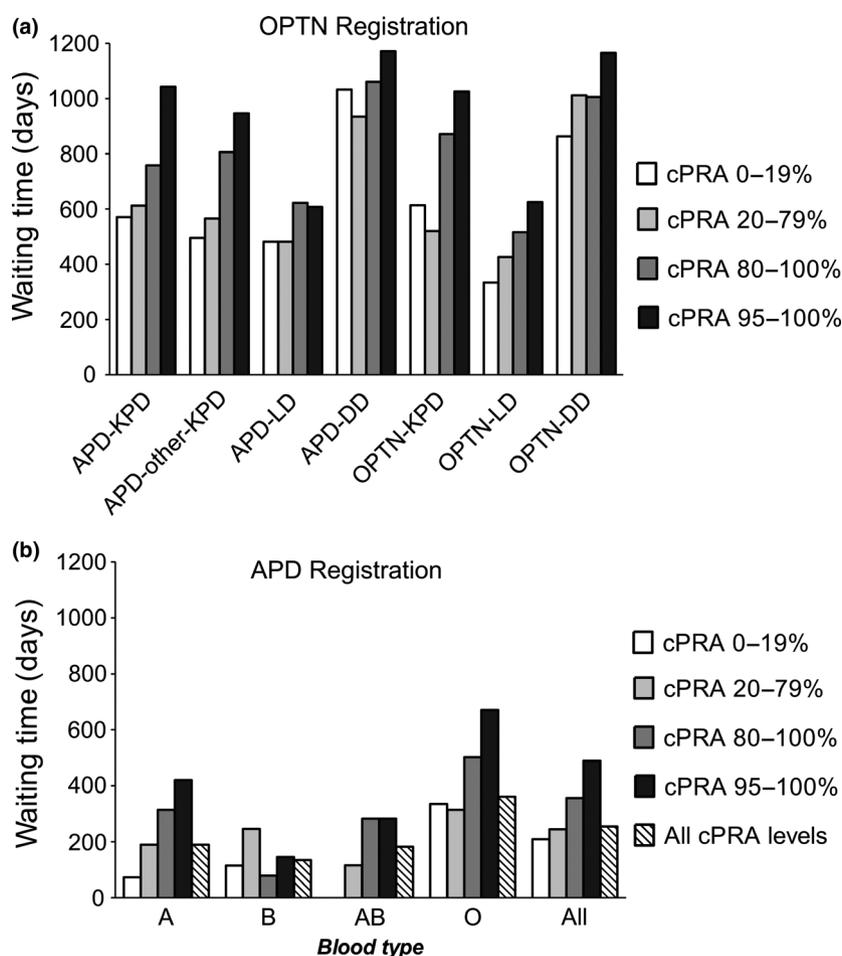
Figure 6 Impact of sensitization and blood groups as well as transplant group (APD-KPD, APD-LD or APD-DD) on the waiting time for transplantation. (a) Patients were stratified by sensitization and transplant group. (b) Patients were stratified by the sensitization level and their blood groups. The waiting times calculated from the day of OPTN-registration is shown in panel a and from the day of APD-registration is shown in panel b. The 2-way ANOVA with interaction was used to examine the relation of cPRA levels in patients with A versus O blood groups on their waiting time.

November 2014, 31 out of 50 recipients (70%) benefited from the new KAS program (prioritizing patients with 98–100% cPRA or being on dialysis ≥ 10 years). Together, 0MM and KAS programs facilitated 69 transplants representing 9.7% of all 712 transplants among APD-registered patients. Since OPTN revealed a similar trend the new KAS benefits exceptionally disadvantaged patients by expanding their access to the large donor pool [32]. Indeed, finding matching donors seems to be the best solution for VHS patients.

The greatest APD challenge was the large fraction of continuously accumulating VHS patients: in a 6-year period over 70% of NonS/MS/HS but less than 50% of VHS found a successful match. Overall APD-KPD found matches for 21% out of all VHS patients, which was similar to 23% in APD-DD. Recently published papers confirmed similar trends in KPD programs [25,33–36]. In one study, 34 out of 35 candidates

(97%) with cPRA 0-94% received a kidney transplant while only 4 out of 30 with cPRA 95-100% (13%) during a 40-month observation period; 28 out of 29 with cPRA 95-100% were still waiting [35]. This confirms the accumulation of VHS patients in KPD programs even with a built-in prioritizing system. In addition to KPD, increased access to a large pool of deceased donors through the new KAS was an important source of kidney transplants for these disadvantaged patients.

Because of good survival results, receiving a kidney transplant by any option is the best even when the donor is 50–64 year-old. While living donors ≥70 year old had higher graft loss [37], living donors 18–64 year old had minimal effect on graft survivals [38]. Similarly, a 30-year donor-recipient difference did not negatively affect a 10-year kidney graft survival [39]. Furthermore, a recent analysis demonstrated an advantage for recipients without and with desensitization: overall, those

receiving a transplant from LDs or DDs survived significantly longer than those remaining on the waiting-list ($P < 0.001$ for both) [8,40]. With desensitization, the 1- and 5-year LD graft survivals were 90.6% and 69.2% for patients with positive T-cell flow crossmatch (FXM) while 87.5% and 72.9% for patients with B-cell positive FXM [41]. Considering the cost, the focus should be on finding FXM-negative compatible donors by most advanced methods for VHS patients, such as high resolution typing, epitope-level matching and acceptable mismatch approaches [42–47].

Based on our analysis, the following conclusions emerge: (i) Availability of different transplantation options for pairs in enrolled in the APD (APD-KPD, APD-other-KPD, APD-LD, or APD-DD) maximized their chances of achieving a kidney transplant; (ii) Both 0MM and KAS programs benefited VHS patients; (iii) NonS/MS/HS/VHS patients had very good survival results comparable to OPTN. Finding a matching donor should become a priority over desensitization due to the latter's high cost and relatively worse outcomes [41,48], but KPD/desensitization should be offered for some VHS patients; and, (iv) The VHS patients may be helped by increasing the donor pool.

Recent reports described individual KPD programs with their own complexity and uniqueness [33,35,49–52]. While demographics of the National Kidney Registry (NKR) were similar to other KPD and UNOS live donor programs, the NKR had 22.7% HS/VHS patients (cPRA > 80%) in comparison to 4.3% among LD in UNOS [51]. This was similar to 22% of transplanted patients with cPRA >80% in APD-KPD (Table 2). The NKR candidates with cPRA 80–97% were 23% and with cPRA >97% were 80% less likely to be matched than ABO-A candidates [52]. Our data found that patients with cPRA >95% waited 420 days for transplants, which was six times longer than 72 days for ABO-A patients (Fig. 6). Thus, NKR and APD-KPD results confirmed the disadvantage for VHS patients. As suggested by the Australian KPD analysis [33], the NKR and APD agree that the best solution for VHS patients is expanding the pool of available donors. The common national KPD list in US and international in European Union may significantly improve chances for compatible exchanges. In addition, the standardization of DSA and crossmatch testing would also minimize the risk of chain breakdown. The Mayo Clinic KPD

experience in three locations with integrated procedures is an example of benefits from close collaboration [35].

We are exploring additional strategies to increase the pool of donors for VHS patients: (i) DDs could initiate KPD chains as the current KAS prioritizes only patients with a cPRA of 98–100% excluding those with a cPRA of 95–97% [53]. Chains initiated by DD may give access to patients with a cPRA of 95–97% and an incompatible willing donor; (ii) Global kidney exchange would expand access to ethnically diverse donors [54]; (iii) The inclusion of compatible pairs in KPD increases the pool of donors [50]; and (iv) Hard-to-match-patients should be offered a combined KPD/desensitization method [55,56]. In fact, the best approach would consolidate KPD/LD/DD exchange programs with selective desensitization for some VHS patients.

Conflict of interest

The authors of this manuscript have conflict of interest to disclose as described by the Transplant International. Michael Rees, Susan Rees, Itai Ashlagi and Alvin Roth have an ownership interest in Rejuvenate Healthcare, LLC which seeks to provide consulting services regarding care for ESRD patients.

Acknowledgements

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1**.** APD-KPD grafts had similar CIT and DGF as comparable OPTN groups.

Figure S2**.** Donors 50–64 year-old may be safely used for KPD kidney exchanges.

Table S1**.** Scoring system for the APD.

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