REVIEW

Kidney exchange strategies: new aspects and applications with a focus on deceased donor-initiated chains

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SUMMARY

Kidney paired donation (KPD) is a valuable way to overcome immunological incompatibility in the context of living donation, and several strategies have been implemented to boost its development. In this article, we reviewed the current state of the art in this field, with a particular focus on advanced KPD strategies, including the most recent idea of initiating living donor (LD) transplantation chains with a deceased donor (DD) kidney, first applied successfully in 2018. Since then, Italy has been running a national programme in which a chain-initiating kidney is selected from a DD pool and allocated to a recipient with an incompatible LD, and the LD's kidney is transplanted into a patient on the waiting list (WL). At this stage, since the ethical and logistic issues have been managed appropriately, KPD starting with a DD has proved to be a feasible strategy. It enables transplants in recipients of incompatible pairs without the need for desensitizing and also benefits patients on the WL who are allocated chain-ending kidneys from LDs (prioritizing sensitized patients and those on the WL for longer).

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Introduction

Since the first application more than 20 years ago [1], kidney paired donation (KPD) has expanded all over the world, with more and more significant numbers. Kidney exchange programmes (KEPs) are acknowledged as an effective solution to address many cases of immunological incompatibility between patients waiting for a kidney transplant and their willing living donors (LDs). AB0 incompatibility (AB0i) or the presence of antibodies directed against human leucocyte antigen [HLA incompatibility (HLAi)] prevents direct donations in more than one in two otherwise suitable donor-recipient pairs [2]. Desensitization in HLAi pairs is associated with suboptimal mid- and long-term outcomes in patients with a positive flow or CDC cross-match, associated with a significantly higher risk of all-cause graft loss and mortality [3]. Outcomes of AB0i kidney transplants are acceptable after adequate desensitization, but a recent meta-analysis found them associated with a higher mortality rate and loss of kidney grafts compared with AB0-compatible transplants in the first 3 years after transplantation. Awareness of the greater risks of infection and graft rejection, as well as the cost-

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effectiveness balance, should make it worth promoting efforts to adopt KEPs [4].

From a very recent overview of current KEPs in Europe (the 27 EU Member States and some other countries), there seem to be three large advanced programmes in the Netherlands, the UK and Spain, plus seven new, smaller programmes in Austria, the Czech Republic, Poland, Belgium, Italy, Portugal and France. Other countries are ready to start or are preparing their KEPs (Scandiatransplant with Sweden, Denmark and Norway, Switzerland, Greece, Slovakia and Romania), while Finland and Iceland have no such kidney exchange activities [5].

National multicentre registries became common in the last decade and are very promising for the purpose of improving transplant rates – as already reported in Canada, Australia and the USA, where the first KPD transplant was performed in 2000. What began as swaps within single centres soon progressed to organized networks, enabling a growing number of transplants through paired donations (reaching 7595 national KPDs as at March 15th, 2020) [6].

n-WAY exchange, domino-paired donation and advanced programmes

The simplest KPD is a two-way exchange between two incompatible pairs, who swap their donors with one another, each obtaining a compatible transplant (Fig. 1a). This model has several logistic and ethical advantages: the risk of donors reneging is avoided because the transplant procedures take place at the same time; and the number of procedures to organize and perform (i.e. cross-matching and surgery) is small, making it feasible at single-centre level. This model can hardly exhaust all possible efficient exchanges among incompatible pairs, however. It seems to work well for pairs with blood type A/B incompatibility, who are easily combined with other pairs with blood type B/A incompatibility. But it cannot benefit blood type 0 recipients with incompatible willing donors with blood type A/B/AB, unless HLAi pairs are enrolled in the programme. In most cases, sensitized transplant candidates with HLAi willing donors have numerous sensitizations, with multiple anti-HLA antibodies, so mutual reciprocity between two pairs is unlikely. In other words, a blood type 0 recipient with a willing type A donor could only find a two-way match with a pair comprising a sensitized type A recipient and a potential type 0 donor – providing the sensitized type A recipient of the second pair has no donor-specific antibodies (DSA) against the type A donor of the first pair.

A three-way exchange model enables the need for reciprocity between the pairs to be partially relaxed, raising the chances for type 0 transplant candidates to find a match. As shown in Fig. 1b, type A or B patients incompatible with their own intended donors because of DSA may find compatible donors in other pairs without the need for reciprocity, and the donation chain stops after involving one additional incompatible pair. Depending on the number of pairs involved (n), this loop can become an n-way exchange, but involving larger numbers of patients makes the organizational process more challenging, and it may be unfeasible to complete all the procedures at the same time, at the same centre.

The best way to bypass the need for reciprocal matching is to use the so-called domino-paired donations. If an altruistic, nondirected anonymous donor offers a kidney, there is no need to close the loop of compatibilities among pairs. The donor of the last pair eventually donates a kidney to a patient on the waiting list (WL) for a kidney transplant from a deceased donor (Fig. 1c) or becomes a bridge donor and waits for another appropriate pair to start a new, nonsimultaneous extended altruistic donor chain (Fig. 1d). The time lapse intrinsic in this latter model raises several issues relating to the risk of donors reneging, and of recipients being left without a kidney. The risk of donors reneging is greater in the case of bridge donors because their paired recipients have already received a kidney and, during the time it takes to schedule a new chain, there may be clinical problems in these recipients or a loss of motivation for the bridge donor to make their donation, or changes in the latter's state of health.

That said, proceeding with donations before completing the transplant in paired recipients, based on list exchanges (Fig. 2), would add to the risk of recipients going without a kidney if a chain breaks down. This situation would require specific allocation policies to prioritize such patients in a deceased donation programme. In 2004, Delmonico et al. reported on a series of 18 list exchanges in the UNOS Region 1, mostly to overcome AB0i issues (16/18 recipients were blood type 0, and 17/18 were not sensitized) [7]. The authors attempted to demonstrate that this approach would not end in a potential depletion of the type 0 deceased donor (DD) kidneys available for patients on the WL. They argued that the effect of type 0 transplant candidates in incompatible pairs bypassing others on the WL is transient because the small initial disadvantage for the latter disappears as soon as an exchange programme has been in place for a period equating to

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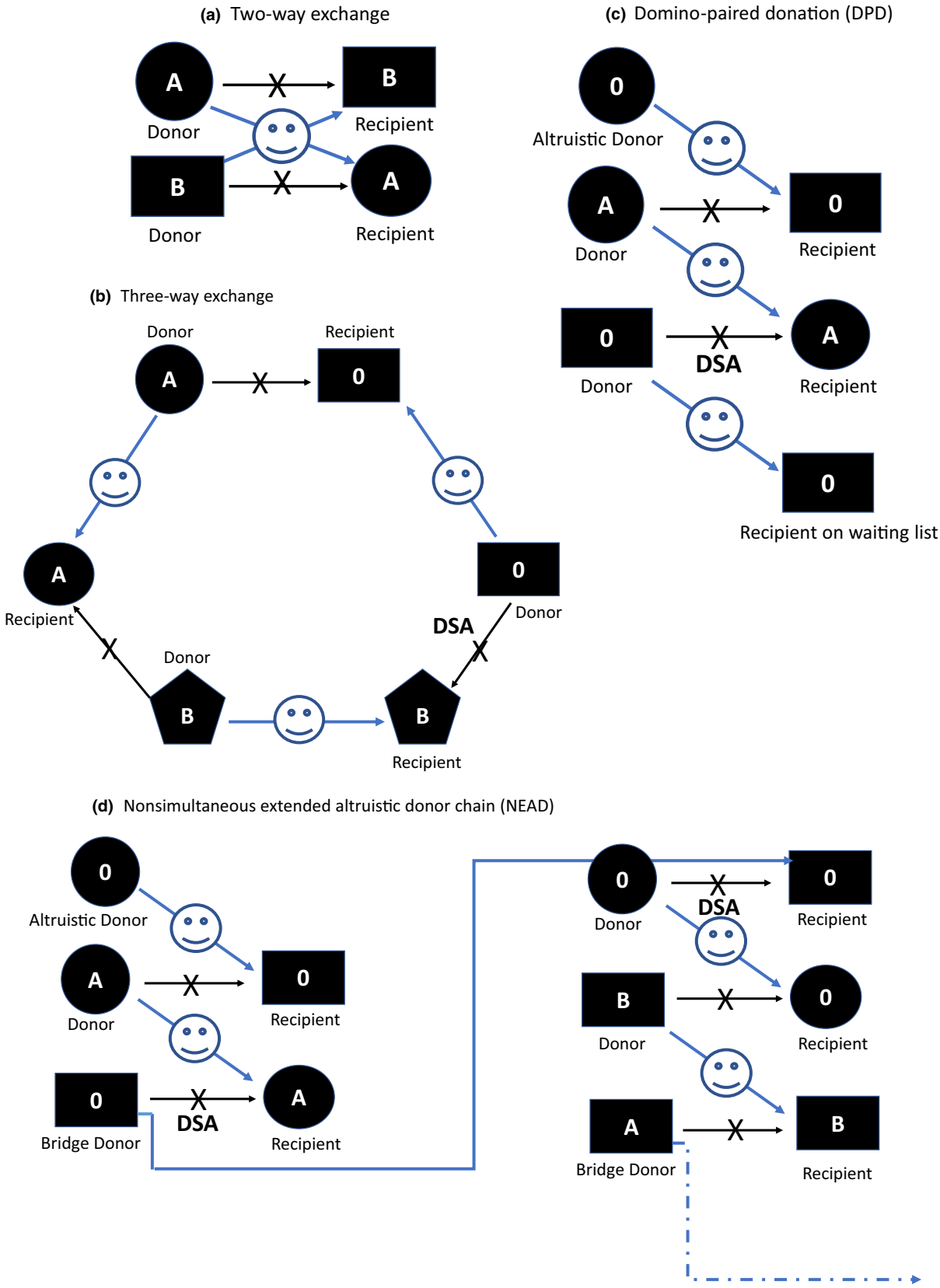

Figure 1 (a) Two-way exchange. (b) Three-way exchange. (c) Domino-paired donation. (d) Nonsimultaneous extended altruistic donor chain.

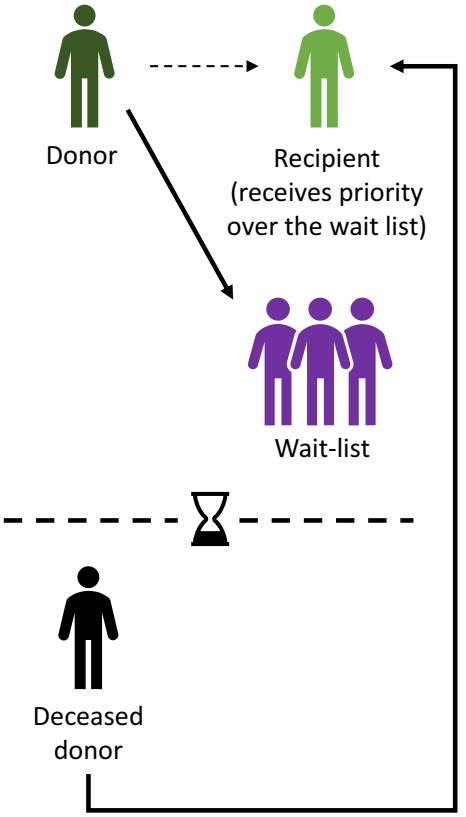

Figure 2 List exchange.

the waiting time threshold for unsensitized type 0 patients. In the reported experience, the waiting time between living donations and DD kidney allocations to recipients in the pair was generally short. The recipients in question were not sensitized, however [max panel reactive antibody (PRA) 29%], whereas waiting times for HLAi pairs could become unacceptably long. For highly sensitized patients, a compatible transplant might even never be found, raising a serious ethical issue.

In 2018, Molmenti *et al.* [8] suggested a very particular type of KPD with a very limited field of application that was used to cope with incompatibilities between DD kidneys and specified intended recipients. In this case, an incompatible pair 'A' would agree to a DD kidney for recipient 'A', and to letting the kidney of donor 'A' go to intended recipient of the willing deceased donors kidney. This solution would be unfeasible in several countries, where allocating a DD kidney to a specific recipient on the WL is not allowed.

Other advanced KPD programmes adopted mainly at single institutions include the so-called 'donation voucher'. As shown in Fig. 3, where there is a 'chronological incompatibility', a willing LD creates a 'voucher' for a future kidney transplant in favour of a designated person with ESRD who does not need it yet. This gives the patient priority for graft allocation if and when they need a transplant [9].

Focus on deceased donor-initiated chains

Melcher *et al.* [10] suggested merging DD programmes with KPD programmes in 2016, an idea explored more recently in a concept paper issued by the Organ Procurement and Transplantation Network (OPTN) [11]. This has also been suggested as a complementary strategy to make multicentric KPD programmes like the NKR (National Kidney Registry, USA) more efficient [12]. As shown in Fig. 4, an incompatible pair participating in the DECeased donor Kidney Paired Exchange (DEC-K) programme agrees to the recipient having a DD kidney (taking a high allocation priority) followed by the LD in the pair donating to an anonymous recipient (a patient on the WL or a recipient in another incompatible pair participating in the programme).

The first report of a deliberate and successful DD-initiated chain was published by our group in 2019 [13], as a pivotal single-centre experience in Italy. With careful management of the several ethical and logistic issues, KPD starting from a DD kidney proved feasible. Such chains are designed to start by giving priority in the allocation of a DD chain-initiating kidney (CIK) to the recipient in a first incompatible pair and to end preferably in favour of a patient on the WL who is sensitized or has been waiting a long time (8 years).

After five successfully completed chains, with a total of 14 kidney transplants starting from 5 DDs, the DEC-K programme was approved for use nationwide by the Italian Transplant Center in July 2019. Three further chains were completed, involving 10 kidney transplants, in the 8 months thereafter. The DEC-K programme has thus enabled 24 transplants (triple the number of DD kidneys employed) in the first 24 months since it was started, implemented at 10 Italian transplant centres and involving 16 incompatible pairs. The chains were short in four cases, enabling two transplants and including one incompatible pair each. The first transplant was from a DD, and the last transplant from a LD was allocated to a WL patient. In the other four cases, the chains were longer, with four transplants being performed and three incompatible pairs involved in each chain.

Deceased donor graft quality was assessed with the Kidney Donor Profile Index (KDPI) and Kidney Donor Risk Index (KDRI). In one case, both kidneys from the same DD were allocated to the DEC-K programme, enabling two chains to start simultaneously. The mean

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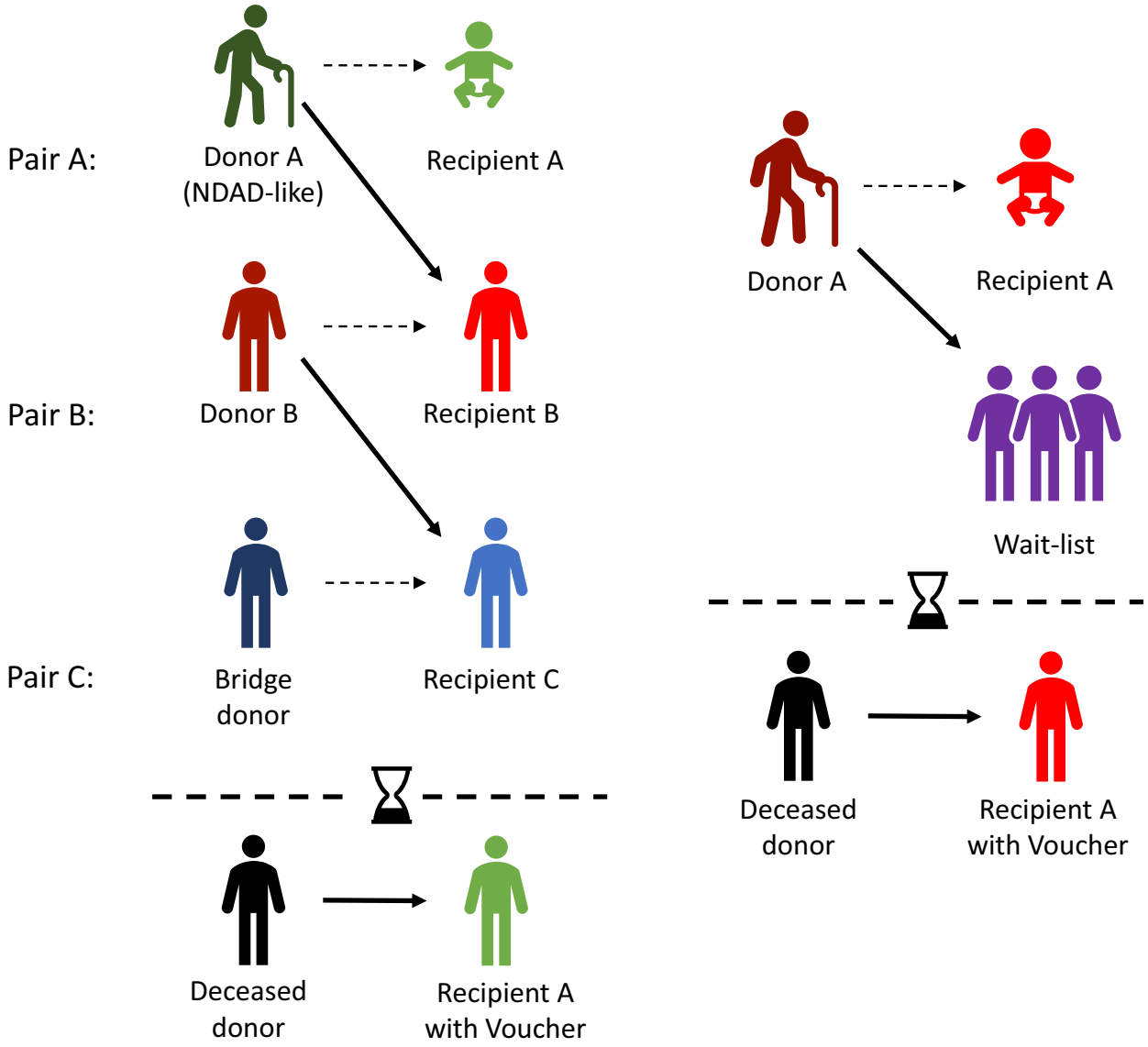

Figure 3 Vouchers for future kidney transplants.

KDPI was 53.5%, and the mean KDRI was 1.07. Donor blood type was 0 in six cases. The mean cold ischaemia time (CIT) was under 8 h. The recipients in the first incompatible pairs of the domino chains took priority for the allocation of CIKs unless there were urgent, highly sensitized patients or candidates for combined transplants (as per the policy of the DEC-K programme described elsewhere [13]).

Table 1 provides details of the recipients of CIKs and the outcome of the related transplants.

Sixteen incompatible pairs across Italy were able to receive and donate a kidney with no need for desensitization thanks to this initial DEC-K experience (seven AB0i and nine HLAi). LD graft quality was assessed with the Living Kidney Donor Profile Index (LKDPI), and it was 16 on average. Six of the 16 LDs were blood type 0, the same number as the blood type 0 CIKs. LDs made their donations a mean 30 ± 24 days after their intended recipients had received their transplant, and none of them reneged.

The main advantage of the DEC-K programme is that it enables recipients in incompatible pairs to receive a compatible kidney transplant, avoiding the need for desensitization, and gaining allocation priority. It also benefits the WL patients who receive chain-ending good-quality kidneys from LDs.

At this stage, in our opinion, the main issues that need to be examined in relation to a wider implementation of the DEC-K programme are as follows:

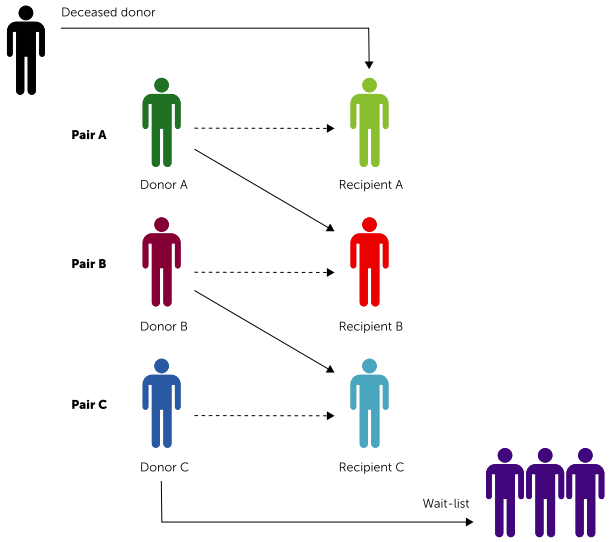

Figure 4 Deceased donor kidney paired exchange (DEC-K) programme.

Depletion of type 0 DD kidneys

The potential depleted availability of these kidneys for patients on the WL for a DD kidney has to be taken into account. In the reported experience, six of eight CIKs came from DDs who were type 0, but there were no WL patients with blood type 0 transplanted at the end of each chain. This is a consequence of pursuing longer domino chains by assigning the six type 0 LDs' kidneys to recipients in AB0i pairs. On the other hand, six LDs with blood type 0 offered their kidney back to the pool, and 10 type 0 recipients were transplanted altogether (four with a CIK, six with a LD kidney) – obtaining a net advantage for the whole pool of recipients.

Logistics

The DEC-K experience confirms that shipping kidneys obtained from KPDs is safe and does not affect graft or patient survival, despite unavoidably longer CITs (as seen in other KPD experiences [14]). The mean CIT in patients receiving DD kidneys was less than 8 h, longer than in the case of recipients of LD kidneys, which averaged under 6 h. No cases of DGF reported, however, suggesting that such CITs do not affect transplant outcomes – possibly partly thanks to the good quality of the donated organs (from both DDs and LDs).

CIK quality

An important issue to consider when applying DEC-K programmes (that needs to be thoroughly analysed and explained to incompatible pairs at the time of their joining the pool) is the difference in quality between CIKs and a potential LD kidney. CIK quality was assessed with the KDRI and KDPI used for DDs. Although these indexes were designed for a different DD population (US donors), and have not been fully validated for the Italian population, they enabled a direct comparison with the LKDPI of each recipient's willing LD. Looking at the results to date (albeit with the drawback of a short follow-up), there were apparently no differences between LD and DD kidney transplant outcomes in terms of renal function.

At the beginning of our DEC-K experience, our selection criteria for CIK eligibility were very strict: donors

Table 1. Characteristics of the first incompatible pairs' recipients and outcome of the related deceased donor kidney transplant.

Chain number	Transplant centre	Age (years)	Sex	Blood type	PRA (%)	Dialysis (months)	Acute rejection	S-Cr at discharge (mg/dl)	CIT (min)
1	#1	53	M	A–	50	10	No	0.81	360
2	#1	50	M	B–	35	0	No	1.4	617
3	#1	28	M	0+	85	44	No	0.67	310
4	#1	41	M	B+	40	10	No	2.29	415
5	#1	71	F	0+	5	1	No	0.95	333
6	#1	61	F	B-	85	67	Yes	1.56	375
7	#1	44	M	0+	0	33	No	1.9	510
8	#1	49	M	0+	52	65	Yes	2.04	740

CIT, cold ischaemia time; PRA, panel reactive antibodies; SCr, serum creatinine.

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at risk of transmissible or neoplastic diseases, or with a history of hypertension or diabetes, or donations after circulatory death were excluded. Donors' serum creatinine also had to be within normal range at the time of the organ procurement, so kidneys from donors with acute kidney injury (AKI) were discarded even if they had no substantial comorbidities, and so were kidneys from donors with a history of hypertension but no evidence of any organ damage. There is growing evidence of donated kidneys with AKI achieving much the same long-term renal function and graft survival rates as those without AKI [15]. Donors with mild hypertension well controlled with antihypertensive medication, and no evidence of organ damage is now considered suitable, not expanded criteria donors [16]. In January 2020, our selection criteria were consequently revised to make them slightly less strict.

Timing

One of the unfavourable aspects of the DEC-K programme that warrants attention and needs to be improved concerns the time taken to start and complete a chain: the time increases with the length of the chain, as more transplant centres and more incompatible pairs become involved. When only one or two centres and only one incompatible pair were involved in the match run, chains took a mean 25 days to complete (range 3–64 days), while longer domino chains took a mean 97 days (range 77–113 days). Such a difference highlights some crucial issues that can affect the success of the programme. First, the risk of LDs reneging could increase if they wait too long before donating. In our DEC-K experience, though none of our LDs failed to donate a kidney, half of them (8/16) waited more than 30 days to undergo nephrectomy (max 85 days). Another concern has to do with the current policy of the DEC-K programme to exclude initiating a new chain until the previous one has been completed. Delays in the completion of a chain thus interfered with the 'rapid allocation' of organs to prioritized recipients, and explain why only a moderately small number of chains have been completed since March 2018, when the programme started.

A better understanding of the logistic and coordination issues will enable the timing between surgical procedures to be optimized, and this would be particularly important in countries larger than Italy.

To conclude, the aim of initiating chains of LD transplantations with a DD is to: (i) optimize the use of resources provided by LDs and increase the number of transplants; (ii) reduce the need for desensitization; and (iii) increase the chances of a transplant for sensitized recipients. This approach should be taken into serious consideration especially in countries where altruistic donations are not allowed or not fully developed, and where the pool of incompatible pairs is too small to obtain effective matching runs with standard KPD programmes.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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