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THE MARGINAL KIDNEY DONOR

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Abstract

Purpose of review: The current era of organ shortage has necessitated a widening of criteria for donation, considering donors that would have been considered unsuitable before. This review summarizes recent advances in strategies to maximize the use of marginal kidneys without compromising outcomes.

Recent findings: Various strategies have been studied and implemented to optimize procurement and allocation of marginal kidneys and to preserve their function. In particular, a growing number of transplant centres are using donors after circulatory death. Whereas normothermic *ex vivo* and post-mortem perfusion are promising strategies to improve outcomes of marginal grafts in the future, dual kidney transplantation is a viable strategy which is at the present potentially underutilized. Despite active research on newer strategies to evaluate organ quality, pre-transplant biopsy assessment currently remains the most reliable method. The practice of using living donors with advanced age is supported by available evidence, whereas the use of living donors with minor medical abnormalities in the youngest ages needs further investigation.

Summary: Progress has been made in recent years, clarifying the best criteria for evaluating, recovering, and allocating marginal kidney donors. However, further research is needed, with special regards to the criteria for using marginal living-kidney donors.

Keywords

Donation after circulatory death; Dual kidney transplant; Marginal living donor; Pulsatile machine; Donor biopsy

Introduction

The increasing disparity between organ supply and demand is progressively extending wait-list time for patients seeking kidney transplantation [1]. In an attempt to combat this trend and to manage the increasing fraction of older donors and of donors with comorbidities,

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Conflicts of interest

The authors have no conflicts of interest to declare.

selection criteria for organ donation have been widened, leading to the use of organs that would have been previously deemed unsuitable. Nowadays, kidneys from deceased donors with older age and comorbidities [1] or donors after circulatory death [2] are being used by a progressively increasing number of transplant centers. Living donors with advanced age or with medical abnormalities are also progressively being transplanted [3]. On the other hand, the use of kidneys from marginal donors is still being questioned because of concerns regarding the risk-benefit ratio of the use of these organs and optimal criteria for allocation. The increasing use of marginal living donors has also raised concerns, mostly regarding the donor's long-term risk after donation [4].

Herein we review recent advances in strategies that are being implemented to maximize the use of marginal kidneys without compromising recipient outcomes. Emerging concerns regarding marginal living kidney donors will also be reviewed.

New allocation policy of grafts from marginal deceased donors

The United Network of Organ Sharing (UNOS) Kidney Transplantation Committee has recently approved a new allocation policy, which will be implemented by the end of 2014 [5], based on the Kidney Donor Profile Index (KDPI), a numeric measure of donor quality. KDPI represents an improvement over the old Extended Criteria Donor (ECD)/Standard Criteria Donor (SCD) dichotomy, by taking into account that not all ECD kidneys are alike. KDPI is a percentile rank, ranging from 1 to 100, based on a number of donor risk indicators (KDPI=85 means that 85% of donors are of better quality). Kidneys with KDPI>85% are offered to a wider geographic area to promote broader sharing and expedite utilization. Transplant programs may choose to accept kidneys of different quality, depending on the medical circumstances of each particular candidate, by establishing candidate-specific KDPI acceptability thresholds [6].

Expanding the donor pool without compromising recipient outcomes:

Donation after circulatory death

Donation after circulatory death (DCD) has regained much attention during the last decade (Table 1) [7]. Thanks to the development of clear legislation and guidelines, DCD is now part of standard clinical practice in ten European nations, as well as in the United States, Canada, Australia, and Japan [7].

Graft function and survival of kidney transplants from DCD donors is comparable to that of donation after brain death (DBD) donors [8], although the former have higher rates of primary non-function and delayed graft function (DGF), leading to higher discard rates in DCD than DBD donors [2]. Concerns regarding DCD donors are particularly related to the increasing proportion of older donors in this group and to the widespread implementation of national or even international allocation policies, resulting in prolonged storage times for kidneys already at increased risk of primary non-function [9]. A recent study showed that donor age of 60 years or higher has comparable effect on survival in controlled DCD and in DBD donors. However, unlike donor age, increased cold ischemia time (e.g. longer than 24 hours) has a detrimental effect on graft survival in controlled DCD but not in DBD [10].

Therefore, kidney transplant from older DCD may be considered a viable option, provided that cold ischemia times are kept short by using DCD kidneys for local rather than national/international allocation [9].

In the UK, where controlled DCD donors represent 40% of the deceased-donor pool [11], the waiting list had a small decline in recent years, despite a plateauing of brain-death donors and living donors [9, 11]. However, the view that the use of DCD universally increases the deceased-donor pool has been recently challenged by a cross-sectional study showing that the number of organs transplanted per donor is significantly lower in DCD than in DBD donors and that, across countries, there is significant correlation between higher DCD and lower DBD rates [12]. In the UK, the increase in living donor transplants (from 7.6 to 16.3 per-million-population) and DCD kidney transplants (from 1.9 to 11.7 pmp) observed from 2003 to 2012 was paralleled by a slight decrease in the number of DBD kidney transplants (from 20.0 to 17.7 pmp) [11]. However, the total number of kidney transplants has actually increased from 1,748 in 2003 to 2,901 in 2012, the increasing trend being maintained in 2013. In UK, the process of maximizing the use deceased-donor marginal kidneys has been greatly enhanced after setting up the Organ Donation Task Force for organ procurement in December 2006 [11].

Dual transplantation

Dual kidney transplantation (transplantation of both kidneys in one recipient) has been proposed [13] to recover marginal kidneys that would otherwise be discarded. The rationale underlying this strategy is that the sum of the viable nephrons in the two marginal kidneys approaches the number in one standard kidney. Despite the excellent results obtained with this strategy [14], dual kidney transplantation has not gained acceptance worldwide, representing only about 2% of transplanted kidneys in the US [15]. Different reasons account for this apparent paradox. Due to the increased perioperative risk, many recipients with cardiovascular disease are not deemed suitable for dual transplantation. However, when dual transplantation is performed in selected recipients, the risk of perioperative and surgical complications is low [4]. Dual kidney transplantation implies the occupation of two iliac fossae, which might be an issue in younger recipients with longer life expectancy and that will likely undergo re-transplantation in the future [16]. However, in some instances (*e.g.*, congruity between the size of the kidneys and the recipient's pelvis, and suitable iliac vessels), dual transplantation can also be carried out with ipsi-lateral placement of both kidneys [16]. Criteria used to decide allocation of marginal kidneys to dual or single transplantation are heterogeneous (Table 2). Despite evidence supporting that the Remuzzi score is well suited for this purpose [14], there is no uniform agreement on the threshold at which dual transplantation should be considered or organs should be discarded [4, 22] (Table 3).

Notwithstanding, dual transplantation is still regarded as a valuable option to expand the pool of marginal donors suitable for transplantation. Tarniover *et al.* have recently estimated that in the US dual kidney transplantation could result in a 12% increase in the number of transplants performed from donors with KDPI>90% [15]. More importantly, dual

transplantation could represent a strategy to use kidneys from DCD donors deemed unsuitable for single kidney transplantation [28].

Organ storage strategies for marginal kidneys

Findings from recent meta-analyses of randomized trials [29–31], conducted either with ECD and/or DCD kidneys suggest that hypothermic machine perfusion (HMP) reduces DGF compared with static cold storage. Consistently, an analysis of 2000–2011 SRTR data from the US [32] showed that HMP had the greatest impact on reduction of cold ischemia-related DGF in ECD transplants, followed by DCD transplants, and then SCD transplants. However, HMP does not reduce the risk of primary non-function or acute rejection, and has no impact on long-term graft or patient survival [29–31, 33]. Given the high costs of HMP, no firm recommendations can be made favoring the use of machine perfusion over standard cold static storage [4].

Normothermic *ex vivo* and post-mortem perfusion, in which the kidney is perfused with circulating, warm, oxygenated blood or an analogous solution, has the potential to limit some of the effects of hypothermic preservation [34], and deliver therapeutic intervention enhancing preservation and restoring function of marginal kidneys [35, 36]. An alternative method involves the use of extracorporeal membrane oxygenation (ECMO), which is often employed as the reperfusion strategy in the setting of uncontrolled DCD [2]. The first series of ECD renal transplants performed after a short period of *ex vivo* normothermic perfusion with an oxygenated red cell-based plasma-free was recently reported [34]. Beyond documenting the feasibility and safety of the technique, the study showed a lower rate of DGF in marginal donor kidneys undergoing *ex vivo* normothermic perfusion compared to the consecutive historical control group of kidneys preserved by traditional cold storage. Further studies are needed to elucidate the most useful applications of normothermic *ex vivo* perfusion for routine clinical practice [37].

Pre-operative assessment of graft quality

Identification of predictors of graft outcome is instrumental in the allocation of marginal kidneys to decrease the risk of discarding viable organs and prevent transplantation of kidneys of inferior quality. Different clinical risk indexes to predict graft outcome have been published, the most recent being generated from US [6] and UK [38] registry data, respectively (Table 4). The US score, which forms the basis of the KDPI computation, is explicitly intended for allocation purposes (see above). However, pre-transplant donor biopsy represents the most reliable tool for marginal organ allocation [36]. Different histopathological or composite clinico-histopathological, and even molecular-histopathological [41, 42] scoring systems have been proposed (Table 4). It is worth mentioning that histologic scores are logistically difficult to implement in the allocation algorithm of many organ procurement organizations. In addition, pre-transplant biopsy assessment, which takes 3–5 hours, may also increase cold ischemia times. Finally, their results may show a great deal of variation between pathologists [43]. To address this latter issue, assessment of soluble biomarkers has been proposed. Human studies have described biomarkers to predict kidney transplant outcomes since the 1970s. A recent systematic

review of these data showed that increased levels of donor urinary biomarkers of kidney injury, such as neutrophil gelatinase-associated lipocalin (NGAL), are associated with DGF and 1-year graft survival [44]. Analyses of the perfusate biomarkers (*i.e.* molecular and cellular components released by the donor into the preservation solution during HMP) found significant associations between elevated levels of various markers, primarily glutathione-S-transferase (GST), and increased risk of DGF [44]. However, it has been argued that GST does not provide sufficient discriminatory power to be used for decision-making regarding kidney discard [45, 46]. Rather, these biochemical parameters could theoretically be combined with HMP characteristics, such as renovascular resistances, which, *per se*, also have inadequate capacity to predict the risk of DGF and early graft survival [35, 47]. It should be highlighted, however, that no study published so far has demonstrated the existence of parameters that can reliably predict the occurrence of primary non function [36].

The marginal living donor

Older individuals and individuals with medical abnormalities, such as hypertension, obesity, borderline HbA1c levels, microalbuminuria, or borderline-normal GFR are increasingly being considered as suitable candidates for donation [3, 4, 48].

Recent large-scale follow-up studies, comparing long-term outcomes of living donors with those of healthy controls in the US [49] and Norway [50], have provided novel evidence concerning long-term risks associated with donation in the average living donor. These studies showed that donation does slightly increase (by +0.2 to +0.5%, depending on donor's race) the risk of future ESRD 15 years post-donation [49, 50]. Moreover, at variance with previous evidence [51], the Norwegian study [50] showed that, even after excluding marginal donors from the analyses, donation increases long-term mortality by about 30%. In this study, the estimates of the relative risk were greatly dampened by the adjustment for confounding factors, casting doubts on the validity of the comparison with the reference healthy population and, therefore, on the presence of residual confounding in the adjusted analyses. Nonetheless, these findings raise concerns regarding the long-term fate of marginal donors, who are potentially at further increased risk compared to average donors.

The risk of ESRD in living donors increases with age up to 0.7% at 15 years in donors aged 60 years [49]. Older age is also associated with a mild increased risk of hospitalization following initial discharge [52], and of procedure-related complications [53]. Nonetheless, mortality amongst living kidney donors aged 70 was no higher than healthy matched controls drawn from the NHANES-III cohort [54]. The outcomes of donors with borderline-normal GFR have not been assessed systematically. Concerning the cut-off for the minimum acceptable GFR in a potential donor, the UK Renal Association and BTS recommend a predicted GFR of at least 37.5 mL/min/1.73m² at the age of 80 after donation [55]. However, this recommendation, which is based on a theoretical model, needs to be supported from the results of long-term follow-up studies showing that this strategy does not jeopardize the donor in the long-term. Moreover low-normal pre-donation GFR becomes risk factor for ESRD in the donors who develop kidney disease post-donation [56].

While various short-term studies exist supporting that marginal donors with isolated medical abnormalities might have negligible added risk after donation, studies including marginal donors who suffer from multiple medical abnormalities are scanty [4]. Recently, Sofue *et al.* [57] examined the effect of isolated high-normal urinary albumin or isolated mild hypertension on the risk of having 1yr-post-donation eGFR being lower compared to the 1mo-post-donation eGFR. Neither abnormality had any effect when taken separately, but the combination of high-normal urinary albumin and hypertension increased by six times (though only numerically) the odds of post-donation eGFR reduction [57]. It is worth mentioning that the risk associated with medical abnormalities should always be assessed keeping in mind donor age, as some minor medical abnormalities acceptable in older donors may not be acceptable in younger donors, especially in black candidates [56]. Rather, as Steiner pointed out [56], centers might consider accepting more older donors with increased diabetic risk or hypertension, while refusing black candidates under the age of 35, or other donors under age 35 with below median GFRs and all but the lowest diabetic risk.

Concerns regarding the use of marginal living donors do not usually consider recipient outcomes as much as donor outcomes. Indeed, recipients of kidneys from older living donors have comparable graft survival to that of recipients of kidneys from deceased standard-criteria donors and better graft survival than recipients of ECD kidneys [54, 58], and donor estimated-GFR does not seem to affect graft survival [59].

Conclusions

The expansion of the waiting lists for kidney transplantation has made the issue of using marginal kidney donors critically relevant. Various strategies have been studied and implemented to optimize procurement and allocation of marginal kidneys and to preserve their function. Altogether, these strategies allowed a steady, albeit minimal increase in the rate of successful transplants, despite the shrinkage of the standard donor pool. However, additional studies will be instrumental to further optimize procurement and allocation of marginal kidneys and to preserve their function, in order to offer suitable grafts to the largest fraction possible of patients in need.

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* of special interest

**of outstanding interest

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*Although based on estimated rather than measured donor GFR, this large scale study shows the validity of the standard rule that a donor GFR below 80mL/min is associated with poor graft outcome.

Key points

- Controlled donation after circulatory death (DCD), now standard practice in many countries, has substantially increased the pool of available donors in UK. It has no adverse effects on graft outcomes, as long as cold ischemia times are kept short.
- Normothermic *ex vivo* and post-mortem perfusion are promising strategies to improve outcomes of marginal graft in the future, whereas more extensive implementation of dual kidney transplantation may increase recovery of marginal grafts
- Pre-transplant biopsy is still the most reliable method to evaluate organ quality. Molecular or functional parameters (*e.g.* derived from normothermic *ex vivo* and post-mortem) might offer new opportunities in the future.
- Living donors of older age or with medical abnormalities are increasingly being considered as suitable candidates for donation, but concerns are still present on the risk of long-term sequelae of young donors with medical abnormalities.

Table 1.

Overview of donation after circulatory death

Definition of DCD	Donation after circulatory death (DCD) is the condition in which kidneys (and other organs) are recovered from donors in whom death is identified by the time when permanent peripheral blood flow cessation occurs, rather than after the complete and irreversible cessation of all brain functions as it occurs with the donation after brain death (DBD) [7].
Controlled vs. uncontrolled DCD	Controlled DCD happens in circumstances where death is anticipated, but has not yet occurred. It may take place in an ICU or special care unit and it is the predominant type of DCD in most Countries [7]. Uncontrolled DCD occurs when a person dies unexpectedly, death being declared upon arrival at the hospital or after unsuccessful resuscitation. This latter type of DCD predominates in France and Spain [7].
Organ reperfusion strategies in controlled and uncontrolled DCD	Prompt organ reperfusion after death is instrumental for the success of DCD. In controlled circulatory death, where the moment of withdrawal of life-sustaining therapy leading to circulatory arrest can be planned in advance, the technique for organ reperfusion are simpler and safer. Most often they consist in midline laparotomy followed by a rapid cannulation of the aorta to start the cold flush [2]. In uncontrolled circulatory death, the procedures are more demanding. After declaration of death, the donor is usually connected to a cardiopulmonary-bypass system by femoral cannulation (e.g. normothermic ECMO, extracorporeal membrane oxygenation) to preserve the abdominal organs before the procedures for organ procurement can be organized [2].

Table 2.

Different criteria for allocating kidneys to dual transplantation.

Reference	Location	Criteria	Comment
Remuzzi, et al. 2006[14]	Italy	Pre-transplant biopsy is performed in all donors>60yrs. Renal pathology is scored from 0 to 3 (none to severe disease) in four areas namely, glomerulosclerosis, interstitial fibrosis, tubular atrophy, and vascular disease. The final Score, which results from the sum of each component, ranges between 0 and 12. Kidneys with score 3 should be accepted as single kidney transplants, those with score 4–6 as dual transplants, and those with score 7 should be discarded.	Does not take into account the clinical characteristics of the donors
UNOS Criteria [17]	US	Dual transplantation is performed if any two of the following occur: 1) Donor age>60yrs; 2) eCrCl<65mL/min; 3) Terminal creatinine>2.5mg/dL; 4) Longstanding hypertension/diabetes; 5) Glomerulosclerosis>15% (if >50%, kidney are discarded)	
Snanoudji, et al. 2009[18]	France	Donor age 65yrs: dual transplantation is performed if best eCrCl is 30–60mL/min, kidneys are discarded if best eCrCl<30mL/min, single transplantation is performed if best eCrCl>60mL/min	Pre-transplant biopsy not used for allocation
De Serres, et al. 2010 [19]	Canada	Donor age 60–74yrs: dual transplantation is performed if glomerulosclerosis>15% (kidneys are discarded if >50%) and terminal creatinine 1.7mg/dL. Donor age 75yrs: kidneys are always used for dual transplantation (discarded if glomerulosclerosis>50% or terminal creatinine>1.2mg/dL)	
Eurotransplant Newsletter 2012[20]	Europe	Donor age 75 yrs: the transplant center is offered the opportunity to perform dual transplantation	The additional criteria of eCrCl<75mL/min has been used in some instances to decide for dual transplant
Pierobon, et al. 2013 [21]	Italy	Remuzzi criteria are used (see above), but with more restricted indications to perform pre-transplant biopsy, as follows: Donor age 70yrs Donor Age between 60–69yrs plus one of the following characteristics: eCrCl 60mL/min, proteinuria 1g/day, diabetes, hypertension with at least two drugs, previous stroke or myocardial infarction	
Tamiover, et al. 2014 [15]	US	UNOS criteria (see above) and/or KDPI>90	Not implemented yet

eCrCl, estimated creatinine clearance; KDPI, kidney donor profile index. No published study has ever compared different allocation systems.

Table 3.
Graft outcomes according to histologic score and suggested thresholds to allocate kidneys from marginal donors

Reference	N	Location	Donor type	3-yrs death-censored graft survival	Reference Category	Suggested threshold	Additional findings
Higher Risk Categories							
Snoeijs, et al., 2008 [23]	52	The Netherlands	DCD 60yrs	Score 4: 70%	Score 3: 87%	Score 4	Primary non function: with Score 4: 35% with Score 3: 6%
Anglicheau, et al., 2008 [24]	191	France	DBD >50yrs	Score 4-6: 70% Score 7: 40%	Score 3: 95%	Not stated	
Fernandez-Lorente, et al., 2012 [25]	115	Spain	DBD >60yrs	Score 4: 76% Score 5: 40%	Score 3: 76%	Score 5	
Carta, et al., 2013 [26]	100	Italy	DBD >60yrs	Score 4-5: 85%	Score 3: 90%	Score >5	Only donors with eGFR 60L/min included. Therefore, score 4-5 can be accepted as single transplant provided that donor's eGFR 60mL/min
De Vusser, et al., 2013[27]	548	Belgium	Unselected	Score 4-5: 82% Score 7: 82%	Score 3: 93%		The seven patients with score 7 had 54% graft survival beyond 4-yrs post-transplantation
Hofer, et al., 2014[22]	174	Austria	ECD	Score 4-6: 72% Score 7: 40%	Score 3: 72%	Score 7	Compared to score 3, score 4-6 had worse crude graft survival beyond 5yrs post-transplantation and worse 1-yr eGFR (44 vs 60mL/min)

Studies reporting outcomes in recipients of kidneys scored according to Remuzzi et al. [14].

“Suggested threshold” refers to the threshold above which the Authors suggested that the kidneys should be either discarded [17,18] (dual transplantation was not considered at their Center) or used as dual transplant [20,21].

DCD, donation after circulatory death; DBD, donation after brain death; ECD, extended criteria donor (i.e. from donors older than 60 years or older than 50 years with at least two additional risk factors, including history of hypertension, high terminal creatinine, or a cerebrovascular cause of death); eGFR, estimated glomerular filtration rate.

Table 4.
Scores developed for the prediction of long-term graft function based on deceased-donor quality.

Score	Components of the score	Comment
Clinical Scores		
KDRI [6]	The version used for allocation purposes is based on 10 deceased-donor variables: age, weight, height, creatinine, ethnicity, hypertension, diabetes, cause of death, HCV-positive donor and donation after circulatory death. KDRI can be computed using the open source calculator available at http://optn.transplant.hrsa.gov/resources/allocationcalculators.asp?index=81	N=69,440 Generated from US registry data. It represents the relative risk of transplant failure from a particular deceased donor compared to the average donor. The discriminatory power ranges between fair to good (based on C-statistic). The Kidney Donor Profile Index (KDPI, see text) results from ranking KDRI from the 1st to the 100th percentile, with reference to a given Organ Procurement and Transplantation Network (OPTN) donor cohort.
UK-KDRI [38]	Based on 5 deceased-donor variables: donor age, history of hypertension, donor weight, days in hospital.	N=7,620 Generated from UK registry data. It is the British equivalent of the KDRI, although it is based on a different and smaller set of variables
Histopathological Scores		
Remuzzi, et al., 2006 [14]	Renal pathology is scored from 0 to 3 (none to severe disease) in four areas namely, glomerulosclerosis, interstitial fibrosis, tubular atrophy, and vascular disease. The final Score, which results from the sum of each component, ranges between 0 and 12.	The most widely used in published literature as a stand-alone tool for the evaluation of marginal kidneys. Easy to implement. Proven to be useful for allocation purposes, although there is no uniform consensus concerning the thresholds for decision making purposes (see Table 3)
Navarro, et al., 2011 [39]	Same as Remuzzi but with vascular disease receiving twice the weight: separate scores (0–3) are in fact given for fibrous intimal thickening and arteriolar hyaline sclerosis; therefore the total score ranges between 0 and 15 (instead of 0 and 12).	N=136 Impressive separation of kidneys with poor outcome (score 5, N=17, i.e. 12.5% of the total) from the others. It has not been used in published literature elsewhere.
MAPI (Maryland Aggregate Pathology Index) - Munivetakappa et al 2008 [40]	Based on the presence of arteriolar hyaline sclerosis (4 points), periglomerular fibrosis (4 points), scars (3 points), glomerulosclerosis 15% (2 points), arterial wall-to-lumen ratio 0.5 (2 points). The score ranges from 0 to 15. Prognostic categories are stratified into 7, 8–11, and 12–15 in order of decreasing graft survival.	N=371 Generated from donors turned down from procurement organizations in US. It is the only histopathological score whose components are weighted based on the results of survival analysis. Requires morphometric measures, which might be problematic to implement in most settings.
Composite Clinico-Histopathological Scores		
Anglicheau, et al. 2008 [24]	Based on donor creatinine 1.7mg/dL, donor hypertension, sclerotic glomeruli 10%; the presence of two factors increase the odds of low eGFR at 1yr (i.e. <25mL/min) 5 times, the presence of all three factors increases the odds by 27 times.	N=313 Not assessed for long-term and graft survival. Internal validation only. It has not been used in published literature elsewhere.
De Vusser, et al., 2013 [27]	Donor age, glomerulosclerosis >10%, 3 times interstitial fibrosis/tubular atrophy (according to Banff classification). Score >60 is associated with about –20% 5-yr graft survival compared to score 60	N=548 Predicts 5-year graft survival. Internal validation only. Most of the total score is represented by donor's age. It might have overlooked the importance of vascular lesions because of the use of wedge rather than core biopsies. It has not been used in published literature elsewhere, as yet.
KDRI, Kidney Donor Risk Index.		