Strategies for an Expanded Use of Kidneys From Elderly Donors

María José Pérez-Sáez, MD, PhD,[1] Núria Montero, MD,[2] Dolores Redondo-Pachón, MD,[1] Marta Crespo, MD, PhD,[1] and Julio Pascual, MD, PhD[1]

Abstract: The old-for-old allocation policy used for kidney transplantation (KT) has confirmed the survival benefit compared to remaining listed on dialysis. Shortage of standard donors has stimulated the development of strategies aimed to expand acceptance criteria, particularly of kidneys from elderly donors. We have systematically reviewed the literature on those different strategies. In addition to the review of outcomes of expanded criteria donor or advanced age kidneys, we assessed the value of the Kidney Donor Profile Index policy, preimplantation biopsy, dual KT, machine perfusion and special immunosuppressive protocols. Survival and functional outcomes achieved with expanded criteria donor, high Kidney Donor Profile Index or advanced age kidneys are poorer than those with standard ones. Outcomes using advanced age brain-dead or cardiac-dead donor kidneys are similar. Preimplantation biopsies and related scores have been useful to predict function, but their applicability to transplant or refuse a kidney graft has probably been overestimated. Machine perfusion techniques have decreased delayed graft function and could improve graft survival. Investing 2 kidneys in 1 recipient does not make sense when a single KT would be enough, particularly in elderly recipients. Tailored immunosuppression when transplanting an old kidney may be useful, but no formal trials are available. Old donors constitute an enormous source of useful kidneys, but their retrieval in many countries is infrequent. The assumption of limited but precious functional expectancy for an old kidney and substantial reduction of discard rates should be generalized to mitigate these limitations.

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The age of patients listed for kidney transplantation (KT) has raised due to the increased age of incident dialysis patients and their improved survival rates.[1-3] In parallel, donor age has also increased in many countries,[4,5] but not significantly in the United States (US).[6,7] Historically, organs from old donors have been optimized in Spain.[8,9] Particularly, age limits have been expanding, so that age itself is not usually a significant limiting parameter. In contrast, although candidates aged 65 years or older make up an increasing proportion of the waiting list in the United States,[6] more than half of available kidneys from donors 65 years or older are discarded in this country,[6] despite their argued benefits.[10-12]

The increase in donor age is associated with reduced graft function and decreased recipient and graft survival.[11,13-15] To minimize this impact, age matching criteria between donor and recipient has been adopted, reasoning that elderly recipients have shorter life expectancy independently of the extended lifetime provided by the graft.[16,17] The use of advanced age kidneys is beneficial for dialysis patients and provide extended survival over remaining listed.[11,18,19] Consequently, given the increasing time in the waiting list and the mortality rates during this period, the use of kidneys from older donors should be encouraged.

We have reviewed the available literature on the use of kidneys from advanced age donors, their outcomes, and the potential strategies to expand their use. In particular, we tried to critically assess what is missing in the field by synthesizing and analyzing the material available.

MATERIALS AND METHODS

Literature Search

Relevant studies were obtained from a systematic literature search. Our start point was the systematic review performed

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[1] Department of Nephrology, Hospital del Mar, Barcelona, Spain.

[2] Department of Nephrology, Hospital Universitari de Bellvitge, L'Hospitalet del Llobregat, Barcelona, Spain.

M.J.P.S. and N.M. contributed equally.

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Correspondence: Julio Pascual, Department of Nephrology, Hospital del Mar, Barcelona, Spain. (julpascual@gmail.com).

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in 2007.[14] The literature search included MEDLINE and EMBASE (2007 to March 2016) within OVID system using the following terms:

1. Kidney Transplantation/.
2. (expand$ or extend$ or old$ or elderly or suboptimal or marginal or KDPI) adj25 (don$).tw.
3. 1 and 2.

The reports' selection was initially focused on retrieving all information about outcomes of kidneys from donors 60 years or older. The search strategy was used to obtain titles and abstracts of studies that may have been relevant to the review. Titles and abstracts were screened independently by 2 reviewers who discarded studies that were not applicable. The same reviewers assessed retrieved abstracts and, if necessary, the full text, to determine which studies satisfied the inclusion criteria. Data extraction was carried out by the 5 reviewers for each of the review sections. Special attention was given to the studies including a comparison between old and younger kidneys. Data on donor and recipient demographics, delayed graft function (DGF), graft function, acute rejection, and patient and kidney graft survival were of particular interest.

In the previously published review, a total of 177 reports were reviewed to extract information.[14] They included observational reports of patients' descriptions and outcomes using expanded criteria donors (ECD) (n = 95), or donors after cardiac death (DCD)-ECD (n = 6), value of donor kidney biopsy (n = 16), pulsatile perfusion (n = 3), dual KT (n = 22), and immunosuppression strategies (n = 18).

In the new search we found 1366 reports, and 1159 were discarded (not related to the topic [n = 957], narrative reviews or editorials [n = 58], observational descriptions of patients and outcomes using ECDs or advanced age donors reporting <100 recipients [n = 24], old living donors [n = 40], multiorgan or pediatric transplantation [n = 29], animal studies [n = 23], duplicates [n = 12], or already in the previous review [n = 16]). Reference lists of clinical practice guidelines, review articles, and relevant studies were also surveyed, and some of their references (n = 8) were used. Finally, the number of reports for full review was 215. They were grouped in outcomes of ECD kidneys (n = 49), Kidney Donor Profile Index (KDPI) policy (n = 4), outcomes of advanced age kidneys (n = 36), value of preimplantation biopsy (n = 32), dual KT (n = 27), impact of recipient age (n = 33), machine perfusion (n = 12) and immunosuppressive strategies (n = 22).

Measures of Effect

A global relative risk analysis summarizing the true effect of the different variables on the outcomes has been done when data could have been obtained from the reports. Statistical analyses were performed using Review Manager version 5.2.

For dichotomous outcomes (mortality, graft failure, and DGF), results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Mean difference was used where continuous scales of measurement were applied to assess the effects of the variables.

EXPANSION OF KIDNEY DONOR POOL, GENERAL CRITERIA TO USE OLD KIDNEYS, AND ALLOCATION STRATEGIES

ECD Allocation Policy

In 2002, the Organ Procurement Transplant Network (OPTN)/United Network for Organ Sharing (UNOS) adopted the ECD allocation policy, establishing an ECD definition based on age and 3 significant risk factors determined by a Scientific Registry for Transplant Research (SRTR) analysis: arterial hypertension history, serum creatinine (SCr) >1.5 mg/dL, or cause of death from cerebrovascular accident.[20,21] ECDs were defined as any donor 60 years or older or 50 to 59 years with at least 2 of the cited risk factors. Each criteria was defined by a relative risk of graft failure that exceeded a relative risk of graft loss of 1.7 compared with a reference group of "ideal donors" aged 10 to 39 years, without hypertension, who did not die of cerebrovascular accident, and with a predonation SCr less than 1.5 mg/dL.[20] During the following decade, this ECD program was evaluated in several studies, reporting an increase in the total number of kidneys procured and a marked variation in different US areas regarding the proportion of candidates listed for an ECD kidney and those who finally got an ECD kidney[22-24] (Table 1). ECD-KT was increasing, however, the significant discard rates for ECD kidneys did not significantly change, with 40% of all ECD recovered kidneys discarded in 2005. This rate has probably been unnecessarily high. The long-term outcome of 170 kidneys refused by at least 2 US centers and subsequently transplanted were compared with 170 KT using kidneys initially accepted.[22] Higher DGF rate, higher primary nonfunction rate, and lower creatinine clearance at 5 years in "marginal" kidneys were noted. However, 5-year patient survival and graft survival were not significantly different, justifying the use of this type of kidneys.[30]

KDPI to Guide Allocation

Recently, the Kidney Donor Risk Index (KDRI) and KDPI were introduced as a refined version of the ECD score.[25] The KDRI is based on 10 donor factors associated with graft survival and estimates the relative risk of posttransplant kidney graft failure from a particular deceased donor compared with the median donor (values, 0.5-3.5). Based on the KDRI, the KDPI establishes the quality of the donor kidneys related to the other kidneys transplanted during the previous year (in percentage).[25,31] The KDPI has also been made part of the "longevity matching" allocation in the United Sates, where the best kidneys are allocated to the recipients with the longest predicted posttransplant survival.[32] This index highlights the fact that there is a large variability in the ECDs, with some standard criteria donors (SCD) having lower estimated quality (higher KDRI) than some ECDs. In fact, in each KDRI interval, survival is not significantly different between ECD and SCD, supporting the conclusion that ECD categorization does not alter graft survival above what is already predicted by the KDRI.[33] Despite the KDRI has been related to poorer graft survival,[26] patients transplanted from donors with the highest KDPI have better survival than their dialysis counterparts.[34]

TABLE 1.

Different kidney allocation policies during the last 20 years

First author [reference]	Year published	Country, period	Number and demographics	Survival
US ECD policy				
Sung[22]	2005	US (UNOS) 2001-2004	Review on the first 18 mo after the new ECD policy (2,079 ECD-KT, 16.7%) vs previous 18 mo (1808, 14.5%)	RR for graft loss did not change (1.99 vs 2.07)
Schold[23]	2006	US (UNOS) 1998-2004	ECDs were 16.2% pre-policy vs 17.9% post-policy	A recipient >65 y had RR 4.2 (vs 18-34) of receiving ECD before the new policy, RR, 7.8 post-policy Adjusted HR for graft loss for ECDs (vs SCDs) 1.73 pre-policy vs 1.83 post-policy; CIT and waiting times did not change
Sung[24]	2007	US (UNOS) 1999-2005	4175 ECD KT performed in 3 y after ECD policy vs 3580 in the preceding 3 y	Among ECD-listed candidates who received a DDKT, only 30% received ECD, the others non-ECD KT. The risk of graft loss was higher for ECD (HR, 1.77). 1 y GS for ECD-listed recipients was 83.6% if ECD KT and 90.4% if non-ECD KT
US KDRI/KDPI policy				
Rao[25]	2009	US (SRTR) 1995-2005	69 440 KT	5 y GS 63% (KDRI, > 1.45) vs 82% (KDRI, < 0.79) and 79% (KDRI, 0.79-0.96)
Han[26]	2014	Korea 1998-2011	362	KDRI > 1.119: HR for graft failure 2.6, better correlated to lower eGFR than ECD
ESP				
Smits[27]	2002	Eurotransplant 1999	209 donor/recipient >65 y (ESP)	1, 5 y PS 91.70% ECD vs 95%, 85% non-ECD
			89 senior controls (recipients > 60 y, donors >65 y)	1, 5 y GS 81.53% ECD vs 91.69% non-ECD
Cohen[28]	2005	Eurotransplant 1994-2003	876 donor/recipient >65 y (ESP) 345 senior controls (recipients > 60 y, donors >65 y)	1 y GS and 1 y death-censored GS 64% and 70% with ESP vs 67% and 71% in usual allocation procedure
Frei[29]	2008	Eurotransplant 1999-2004	1406 donor/recipient >65 y (ESP) 1687 recipients 60-64 y who received donor at "any" age (A/O)	5 y PS 60% (ESP), 74% (A/O), 71% (O/A) 5 y GS 47% (ESP), 64% (A/O), 51% (O/A)
			446 donor ≥65 y to any recipient (O/A)	5 y DCGS 67% (ESP), 81% (A/O), 67% (O/A)

A, Studies Assessing Kidney Transplantation Practices in the United States Before and After Implementation of ECD Policy in 2002. B, The KDRI and KDPI recently used in the US. C, ESP old-for-old program reports.

HR, hazard ratio; CIT, cold ischemia time; DDKT, deceased donor kidney transplantation; GS, graft survival; PS, patient survival; CCr, creatinine clearance; eGFR, estimated glomerular filtration rate.

Eurotransplant Senior Program

The Eurotransplant Senior Program (ESP) is a donor-to-recipient age matching policy developed in central Europe in 1999.[27] The 5-year data showed no difference between patients who received grafts from elderly donors via ESP and those who received younger kidneys via the usual HLA-driven allocation. ESP data suggest that if care is taken to avoid the accumulation of additional risk factors such as long cold ischemic time and previous sensitization, old-for-old allocation can be operated successfully.[27-29,35]

All the reviewed allocation strategies with expanded kidney donor pools are summarized in Table 1.[22-29,35] The outcomes of end-of-life care, critical care access (for donors), survival on dialysis, and transplant outcomes vary hugely from country to country. As a result, it is exceedingly difficult to compare what strategy to adopt for "marginal donor organs" by comparing the results of 1 country to another.

DONORS AFTER CARDIAC DEATH WITH EXPANDED CRITERIA

The particular group of ECD-DCD constitutes an increasing source of kidneys suitable for transplantation in many countries. They represented 14% of DCD in 2004 in the United Kingdom and increased to 43% in 2013.[36] In Spain, controlled DCD constitute the most increasing donor modality.[4] However, recent data show that around 50% of ECD-DCD kidneys in the United States are discarded compared with 30% to 40% of brain-dead ECD. Additionally, there is a significant overlap in KDRI scores among ECD-DCD kidneys that are discarded versus those used. This suggests that there may be a significant number of discarded ECD-DCD kidneys that could be acceptable for transplantation.[37] Some reports have analyzed outcomes in Japan,[38] the United States,[39-41] and the United Kingdom[42] (Table 2). In Japanese reports, as it occurs with brain-dead ECD,

TABLE 2.

Reports describing outcomes in kidney transplantation using organs from ECD after cardiac death (DCD)

First author (reference)	Year published	Country, period	Number and demographics		Clinical outcomes and survival	
			Non–ECD-DCD	ECD-DCD	Non–ECD-DCD	ECD-DCD
Teraoka[38]	2004	Japan KT Network 1995-2003	727	552	1.5 y GS 86.2,75%	1, 5 y GS 81.8%, 65%
Locke[39]	2007	US (UNOS) 1993-2005	2562 DCD		5 y GS 81.6%	5 y GS 65.9%
Doshi[40]	2007	US (UNOS)	1048	129	No 5 y GS differences (RR for graft loss, 1.05 in ECD-DCD, $P = 0.23$) 5 y PS 93.8%; 5 y DCGS 96.8%; 5 y PS 96.5%; 5 y DCGS 94.4%	
Singh[41]	2013	US (SRTR) 2000-2011	50 242 non-ECD/non-DCD	12 172 ECD/non-DCD 562 ECD/DCD (median KDRI, 3.94)	1, 5 y PS 92.79%; 1, 5 y GS 82.59%	1, 5 y PS 87%, 81%; 1.5 y GS 74%, 57% ECD status did not modify the greater risk of DGF, PNF or graft loss in DCDs
Summers[42]	2013	UK Transplant Registry 2005-2010	4840 non-ECD/DCD 4663 DBD vs 1827 DCD (426 donor ≥60 y)		1 y PS 93.1, 89.1%, 1 y GS 80.2, 84.5%	1 y PS 90.8%, 93%, 3, 1 y GS 75.9%, 77.8%
					eGFR 50.9 and 53.6 mL/min	eGFR, 41.9 and 40.9 mL/min
					Similar PS and GS between DBD and DCD	DCD, ≥60 y; HR, 2.35 (graft loss) compared with DCD <40 y, similar GS compared with DBD ≥60 y
				DCD, OR = 1.49 (PNF) and 3.08 (DGF), with lower eGFR at 12 mo DCD with CIT > 24 h, HR = 2.36 (graft loss)		

DBD, donor after brain death; OR, odds ratio; PNF, primary nonfunction; DCGS, death-censored graft survival.

kidney grafts from ECD-DCD show inferior survival than those from standard DCD.[38] However, the US Registry has pointed out that DGF, primary nonfunction and graft survival rates are not different between DCD-ECD and DCD-non-ECD when adjusted with multivariate analyses.[40,41] The UK experience remarks a double risk of graft loss among ECD-DCD transplants compare to those younger than 40 years in the multivariate analyses, but similar graft survival than brain-dead ECD.[42] An update of the UK Registry shows similar rates of primary nonfunction, 5-year estimated glomerular filtration rate and 5-year graft survival between ECD-DCD and brain-dead ECD KT.[36] The report of graft losses and survival allowed to calculate RRs for 1- and 5-year graft loss[38,41,42] (Figure 1). The events pooled are raw unadjusted ones. The RR for graft loss is higher with ECD-DCD than with non–ECD-DCD at 1 year (RR, 1.60 [1.28-1.99], $P < 0.0001$) and 5 years (RR, 1.62 [1.22-2.16], $P = 0.0009$).

Consequently, graft survival is lower using ECD-DCD than using non-ECD-DCD, but still reasonable to stimulate the use of this donor source. An effort should be made in selecting donors with enough kidney function potential, but based on the evidence available, selection criteria for DCD donor kidneys should not be different to those applied to brain-dead donor kidneys.

OUTCOMES: WORSE PATIENT AND GRAFT SURVIVAL WITH ECD KT OR ADVANCED AGE DONORS

ECD Versus SCD

Some observational studies have suggested that patient and graft survival achieved by using ECD kidneys are similar to those obtained with SCD (**Table S1, SDC,** http://links.lww.com/TP/B387)[43–49]. However, the majority of 1-center studies,[43-56] and all available multicenter or registry reports[20,57-74] show significantly worse graft survival for ECD kidneys, with an increased risk of graft failure (**Tables S2 and S3, SDC,** http://links.lww.com/TP/B387). The differences in outcomes regarding patient survival

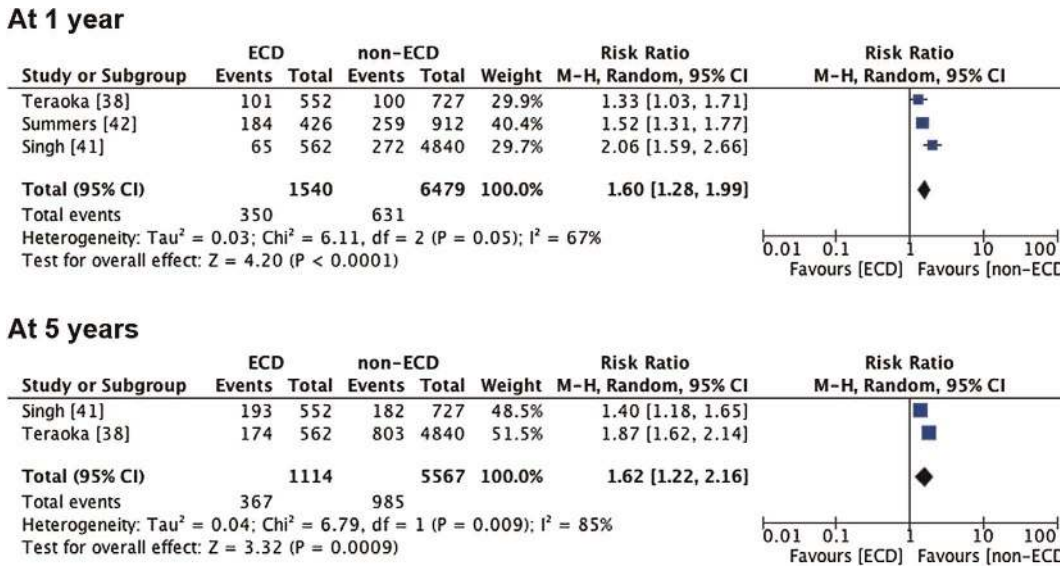


FIGURE 1. Higher risk of graft loss using organs from ECD vs non-ECD after DCD.

and death-censored graft survival after KT using ECD versus SCD are more variable. Great difficulties emerge when ECD KT outcomes are analyzed because all aspects in this area tend to be multifactorial and subject to great variability. The 1-center analyses are mainly European, and the multicenter reports mostly come from the consecutive publications from the UNOS registry. Graft survival is consistently decreased but patient survival and death-censored graft survival using ECD kidneys are not always worse, especially among older recipients.[63,65,67,73] Other important outcomes using kidneys from ECD have been analyzed. In general, higher rate of DGF,[64,73] primary nonfunction,[60,64] and acute rejection have been described. Furthermore, worse kidney graft function has been the rule.[66,71,73,75,76]

Very Advanced Age

A few studies with the intention of stepping forward in the expansion of kidney donor pool have emerged from Europe in the last years reporting similar results with kidneys from very advanced aged donors (>70 or >75 years) than from traditional ECD kidneys (Table 3).[19,63,77-84] Some of these reports contain numerical data that allowed us to calculate RRs for DGF,[19,63,78,80,81,83] graft loss at 1 year[19,63,77-82] and 5 years[19,63,77,79,81,82] and mortality at 1 year[19,63,77-81,83] and 5 years[19,63,77,79-81] (Figure 2). DGF rates were similar in patients receiving a kidney from a very advanced age donor than in those receiving a kidney from a standard ECD (RR, 1.05 [0.92-1.21], $P = 0.47$). Graft loss was more frequent using a kidney from a very advanced age donor than a usual ECD one at 1 year (RR, 1.55 [1.12-2.15], $P = 0.008$) and 5 years (RR, 1.38 [1.04-1.84], $P = 0.03$). Mortality was also higher at 1 year (RR, 2.43 [2.07-2.86], $P < 0.00001$] but only marginally different at 5 years (RR, 1.41 [0.95-2.08], $P = 0.08$) (Figure 2). All these pooled analyses are performed including raw data, unadjusted by confounding factors, or multivariate analyses.

ECD Versus KDPI

The OPTN/SRTR 2013 report[76] is the last one published that depicted the deceased donor waiting list and waiting times under the previous US allocation system based on the classical deceased donor categories: SCD, ECD and DCD. Recently, Grams et al[85] described that ECD listing by Merion's recommendation[86] is about 50% in the United States, despite the increasing evidence of improved survival in certain dialysis populations when an ECD donor is used compared with remaining on dialysis. Using the classical system, 3-year graft survival for ECD kidneys is 75%, and 5-year graft survival is 64%. Using the newest KDPI cuts, 3-year graft survival for KDPI greater than 85% kidneys is 72% and 5-year graft survival 58%.[76]

Increasing cold ischemia time is a risk factor for DGF among ECD KT, but DGF does not have a significant effect on graft survival: it is likely that many ECD kidneys not considered viable may be useful.[87] In addition, donor/recipient size matching is important to optimize results using ECD kidneys.[75]

OUTCOMES: BETTER SURVIVAL AFTER KT WITH ECD OR ADVANCED AGE DONOR KIDNEYS THAN WAITLISTED AND ON DIALYSIS

Given the worse results with an ECD kidney than with an SCD, it is important to clarify if there is better patient survival using ECD kidneys compared with remaining on the waiting list on dialysis (Table 4).[11,18,19,23,34,86,88-94] This is difficult to assess as the comparison between both populations implies unbridgeable biases. Ojo et al[18] demonstrated that the average increase in life expectancy for recipients of "marginal" kidneys (defined then as those procured from old donors, with comorbidities, such as hypertension or diabetes or with prolonged cold ischemia time) compared with the waiting list nontransplanted dialysis cohort was 5 years, although there was an increase in the early mortality risk after transplant. Soon after this publication, the ECD definition was adopted trying to avoid the term "marginal" and to standardize this type of kidney. Years later, Merion et al[86] studied survival benefit of KT using ECD compared with remaining on the waiting list or getting transplanted with an SCD. Due to excess mortality in the perioperative period, the ECD recipient survival did not equal the survival observed with SCD or

TABLE 3.

Studies showing outcomes in kidney transplantation using kidneys from very advanced age compared with traditional ECD or standard donors

First author (reference)	Year published	Country, period	Number and demographics		Clinical outcomes and survival			
			Very advanced age	Non–ECD/ECD	Graft function		Survival	
					Very advanced age	Non–ECD/ECD	Very advanced age	Non–ECD/ECD
Chavalitdhamrong[63]	2008	US (UNOS) 2000-2005	601 KT from donors ≥70 y	8979 KT from donors 50-69 y	Similar DGF rate (60.4 vs 63.9%, NS) and SCr (12 m) 2.1 vs 1.9 mg/dL ($P = 0.022$)		Adjusted HR for PS 1.37 vs 50-69 y and 1.21 vs 60-69 y aHR for DCGS 1.31 vs 50-59 y and 1.18 ($P = 0.106$) to 60-69 y	
Gavela[77]	2009	Spain 1996-2008	53 ≥ 70 y	201 (55-70 y)	DGF 46%	DGF 44.2%	1, 5 y PS 93,88% 1, 5 y GS 88,70%	1.5 y PS 96,88% 1.5 y GS 89,75%
Collini[78]	2009	Italy 2000-2008	16 single KT, 22 dual KT from donors ≥75 y	154 < 75 y	1 y SCr 2.47 mg/dL		1, 2, 3 y PS 81.2,81.2, 81.2% 1, 2, 3 y GS, 73.3%, 69.8%, 64% (not better with dual KT)	1,2,3y PS 92.1,91.4,89.5% 1,2,3y GS 82.3,77.8,71.4%
Foss[79]	2009	Norway 1993-2007	54 ≥ 75 y		PNF 3.7%; DGF 35%; SCr 163 μmol/L (23 mo)		1, 3, 5 y DCGS 81%, 75%, 59% 1, 3, 5 y GS 77%, 72%, 59% 1, 3, 5 y PS 87%, 83%, 83%	
Giessing[80]	2009	Germany 1999-?	18 ≥ 75 y	73 ≥ 65 y (a) 30 non-ECD (b)	DGF 46%	DGF 36 (a) and 33% (b)	1, 3, 5 y PS 95%, 83%, 83%	1, 3, 5 y PS 95%, 83%, 83% (a) 95%, 83%, 83% (b) No differences in GS No differences in GS
Galeano[81]	2010	Spain 2000-2009	70 ≥ 70 y	159 (50-70 y) 171 (<50 y)	1 y eGFR 39.5 mL/min	1 y eGFR 42.6 (50-70 y) and 58.4 mL/min (<50 y)	1, 3, 5 y PS 90%, 86%, 86% 1, 3, 5 y GS 81%, 81%, 70%	1, 3, 5 y PS 98%, 97%, 96% (<50 y) and 94%, 92%, 85% (50-70 y) 1, 3, 5 y GS 86%, 83%, 81% (<50 y) and 88%, 83%, 74% (50-70 y)

Gallinat[82]	2011	Germany 2001-2009	41 single KT (>75 y) 11 dual KT (>75 y)				81% GS (30 mo), better with dual KT	
Marconi[83]	2013	Portugal 1983-2001	82 (donors >70 y)	1151 (donors <70 y)	1 y Scr 1.9 mg/dl DGF 31.3% AR 11%	1 y SCr 1.5 mg/dL DGF 31.3% AR 14.1%	1, 3, 4 y PS 91%, 87%, 87% 1, 3, 4 y DCGS 87%, 79%, 72%	1, 3, 4 y PS 95%, 92%, 91% 1, 3, 4 y DCGS 90%, 85%, 83%

Note: To convert serum creatinine in mg/dL to mol/L, multiply by 88.4.
DCGS, death-censored graft survival; AR, acute rejection.

remaining on the waiting list until 3.5 years after KT, in terms of cumulative mortality. In other words, according to data published more than a decade ago, it took 3.5 years to justify an ECD KT in terms of survival when this practice was compared with waiting until an SCD was available. The subgroups that showed significant ECD survival benefit included patients older than 40 years, non-Hispanics, unsensitized, recipients with hypertension, and diabetics, particularly in those programs with long (>4 years) waiting times.[86] The long-time waiting for an SCD KT is a risk factor for patient mortality.[89]

Albeit the benefits are clear for certain patient populations,[23,91,92] patient survival is limited when an ECD KT is performed in high-risk recipients, such as retransplantation.[90] Patients 60 years or older with associated comorbidities have particularly suboptimal survival results when receiving an ECD KT compared with SCD KT.[93] Another study found similar results and high-risk recipients that receive an ECD KT, achieved equal survival at 521 days after transplant.[94] The results about higher early mortality with an ECD transplant versus dialysis are consistent in the literature ranging the period to equal survival from 1.7 months to more than 1 year.[18,34,88]

In an attempt to minimize confounding factors in a comparison between patients listed who remained on dialysis and those who are transplanted, our group performed a paired-matched analysis between 823 recipients from donors over 65 years and counterparts listed with the same comorbidity. The risk for death was 2.66-fold higher in the dialysis group.[11] Consequently, ECD-KT shows survival advantage over dialysis in the elderly, although undoubtedly SCD offers better survival. In a further analysis, a cohort of 389 KT recipients from donors 75 years or older was analyzed and compared with those who remained listed on dialysis. Even using these extreme aged kidneys, the benefit in survival over dialysis was clear, with 60% less mortality in the transplanted group. Notably, the youngest recipients, those younger than 65 years, obtained the highest benefit.[19]

Three of the referred studies were enough homogeneous and gave numerical data to calculate RRs for mortality at 1 and 5 years after KT with an ECD or an advanced age kidney in comparison with remaining in the waiting list on dialysis.[11,86,92] Mortality at 1 year was quite similar in patients receiving an ECD/advanced age kidney or remaining on dialysis (RR, 0.49 [0.21-1.15], $P = 0.10$) but decreased at 5 years in those transplanted (RR, 0.47 [0.43-0.53], $P < 0.00001$) (Figure 3).

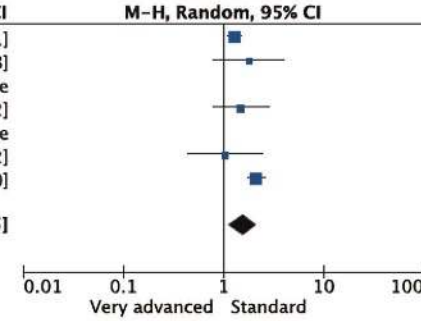
OUTCOMES: EFFECT OF RECIPIENT AGE

Patients older than 65 years represent the fastest growing group on the waitlist in the United States with the numbers increasing from 12.9% in 2003 to 21.2% in 2014.[6] This trend, although encouraging, fails to highlight the low rate of elderly patients waitlisted or transplanted. For instance, less than 5% of dialysis patients older than 65 years are on the waiting list in the United Kingdom and only 10% are transplanted in the first 5 years.[95] This patient population brings with them a unique set of problems, including frailty, cognitive impairment, and comorbidities less commonly seen in the other age groups.[96] All these factors have been associated with morbidity and mortality after

Graft loss at 1 year

Study or Subgroup	Very advanced Events	Total	Standard ECD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chavalitdhamrong [71]	128	601	1491	8979	32.4%	1.28 [1.09, 1.51]
Collini [85]	5	16	27	154	11.3%	1.78 [0.80, 3.98]
Foss [86]	12	54	0	0		Not estimable
Galeano [88]	13	70	20	160	15.0%	1.49 [0.78, 2.82]
Gallinat [89]	13	41	0	0		Not estimable
Gavela [84]	6	53	22	201	10.4%	1.03 [0.44, 2.42]
Pérez-Sáez [19]	84	389	561	5497	30.9%	2.12 [1.72, 2.60]
Total (95% CI)		**1224**		**14991**	**100.0%**	**1.55 [1.12, 2.15]**
Total events	261		2121			

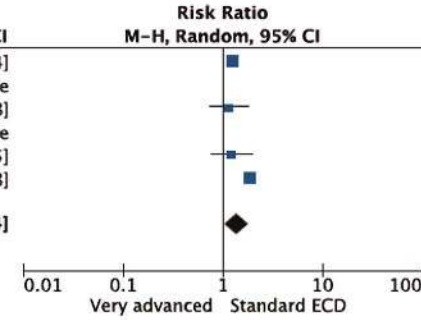
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 15.33$, df = 4 (P = 0.004); $I^2 = 74\%$
Test for overall effect: Z = 2.64 (P = 0.008)



Graft loss at 5 years

Study or Subgroup	Very advanced Events	Total	Standard ECD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chavalitdhamrong [71]	337	601	4050	8979	32.6%	1.24 [1.15, 1.34]
Foss [86]	22	54	0	0		Not estimable
Galeano [88]	21	70	42	160	18.5%	1.14 [0.73, 1.78]
Gallinat [89]	35	41	0	0		Not estimable
Gavela [84]	16	53	50	201	17.4%	1.21 [0.75, 1.95]
Pérez-Sáez [19]	176	389	1347	5497	31.5%	1.85 [1.64, 2.08]
Total (95% CI)		**1208**		**14837**	**100.0%**	**1.38 [1.04, 1.84]**
Total events	607		5489			

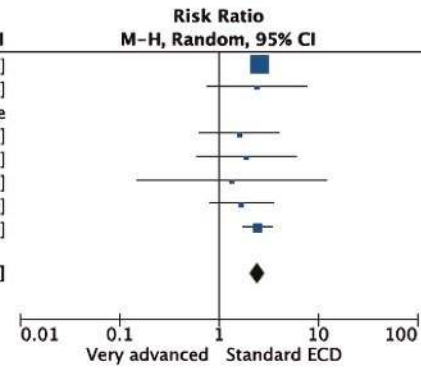
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 31.65$, df = 3 (P < 0.00001); $I^2 = 91\%$
Test for overall effect: Z = 2.21 (P = 0.03)



Mortality at 1 year

Study or Subgroup	Very advanced Events	Total	Standard ECD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chavalitdhamrong [71]	93	601	539	8979	62.9%	2.58 [2.10, 3.16]
Collini [85]	3	16	12	154	2.0%	2.41 [0.76, 7.64]
Foss [86]	10	54	0	0		Not estimable
Galeano [88]	7	70	10	160	3.1%	1.60 [0.63, 4.03]
Gavela [84]	4	53	8	201	1.9%	1.90 [0.59, 6.06]
Giessing [87]	1	18	3	73	0.5%	1.35 [0.15, 12.24]
Marconi [90]	7	82	58	1151	4.6%	1.69 [0.80, 3.59]
Pérez-Sáez [19]	39	389	225	5497	24.9%	2.45 [1.77, 3.39]
Total (95% CI)		**1283**		**16215**	**100.0%**	**2.43 [2.07, 2.86]**
Total events	164		855			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.47$, df = 6 (P = 0.87); $I^2 = 0\%$
Test for overall effect: Z = 10.77 (P < 0.00001)



Mortality at 5 years

Study or Subgroup	Very advanced Events	Total	Standard ECD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chavalitdhamrong [71]	251	601	2631	8979	31.6%	1.43 [1.29, 1.57]
Foss [86]	22	54	0	0		Not estimable
Galeano [88]	10	70	24	160	16.3%	0.95 [0.48, 1.88]
Gavela [84]	6	53	24	201	12.9%	0.95 [0.41, 2.20]
Giessing [87]	3	18	15	73	8.8%	0.81 [0.26, 2.50]
Pérez-Sáez [19]	116	389	687	5497	30.4%	2.39 [2.02, 2.82]
Total (95% CI)		**1185**		**14910**	**100.0%**	**1.41 [0.95, 2.08]**
Total events	408		3381			

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 32.14$, df = 4 (P < 0.00001); $I^2 = 88\%$
Test for overall effect: Z = 1.72 (P = 0.08)

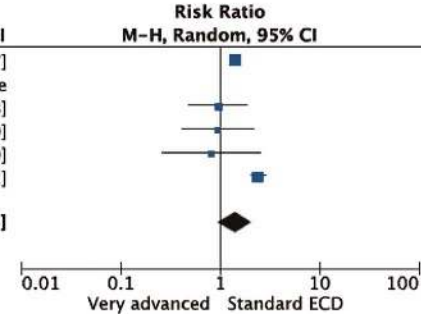


FIGURE 2. Outcomes using kidneys from very advanced age compared with classical ECDs.

transplant,[97-99] although the trend has improved.[100] However, a number of studies have shown improvement in overall life expectancy (mortality risk, 40-60% lower) for those who have received a KT compared with those who remain listed on dialysis,[11,18,19,23,34,86,91,92,94,101,102] even despite higher incidence of early mortality in some reports.[18,86,93,94,101] A number of European and US studies (**Table S4, SDC,** http://links.lww.com/TP/B387)[15,17,27-29,48-50,103-113] have

TABLE 4.

Main studies assessing the benefit on survival of kidney transplantation over dialysis using ECDs or donors with advanced age

First author (reference)	Year published	Country, period	Number and demographics	Mortality risk
Ojo[18]	2001	US (UNOS) 1992-Jun 30 1997	122 175 listed patients, 7454 received a marginal KT (donor >55 y or DCD or CIT >36 h or AH/DM >10 y) vs non-KT on WL	Global RR = 0.75 with "marginal" KT Higher early mortality risk (531 days to equal survival) 5 y PS 77% vs 85% and 5 y GS 59% vs 72% Average increase in life expectancy = 5 y; expected life-years were 15.3 (listed), 20.4 (marginal), 28.7 (ideal) Donor age predicts PS (5% lower each decade)
Puig[88]	2001	Spain 1990-1999	282 (donors >65 y) and 2425 (donors < 65 y)	1, 3, 6 y PS 89%, 85%, 74%, vs 93%, 83%, 62% in nontransplanted dialysis patients 1, 3, 6 y GS 82%, 69%, 45%; 1, 3, 6 y censored-for-death GS 92%, 82%, 61%
Schnitzler[89]	2003	US (UNOS) 1995-1999	33,503	Life expectancy assessment: the wait time for a SCD that equates the expected outcomes of accepting an ECD with waiting for a SCD is 3.2 y (mean) Recipient age had impact: this wait time is 4 y for <30 y, 3.3 if 30-45, 2.2 if 45-60 and 11 mo if >60 y
Merion[86]	2005	US (SRTR) 1995-2002	109,127 listed patients, 7,790 ECD-KT vs non-KT on WL	Global RR = 0.83 with ECD KT Mortality risk for ECD-KT higher than WL until 33rd week, lower thereafter, and equal at 3.5 y ECD-KT lower mortality than WL/SCD-KT if age >40 y, diabetes or waiting time >1350 d Proposal for algorithm of ECD listing
Schold[23]	2006	US (UNOS) 1995-2004	?	Life expectancy for 18–39 y receiving SCD after 4 y of dialysis higher than with an ECD after 2 y (26.4 y vs 17.6 y) but not for recipients >65 y (5.6 y vs 5.3 y) 47.5% of all candidates were listing for ECD
Miles[90]	2007	US (UNOS) 1995-2004	9641 patients with graft loss relisted, 2908 *retransplantations*, 292 with ECD	No survival after ECD retransplantation in comparison to remain in waiting list for a standard donor or remaining on dialysis (HR, 0.98). Standard retransplantation reduced death risk (HR, 0.44)
Rao et al[91]	2007	US (UNOS) 1990-2004	5667 potential recipients ≥70 y listed, 2078 received a DDKT (688, 33% ECD)	KT recipients had lower death RR than dialysis (0.59), even if ECD-KT (0.75) or diabetes (0.53)
Savoye[92]	2007	France 1996-2004	3001 potential recipients ≥60 y listed, 2008 received DDKT (1577, 52% ECD)	HR of 2.31 for death among patients who remained on dialysis compared with those who received an ECD-KT
Kauffman[93]	2007	US (UNOS) 1997-2002	8895 recipients ≥60 y (2342–26.3%-ECD KT)	Recipients ≥60 y that received ECD KT had 90 and 365 days mortality of 6% and 14.4%, respectively. Early mortality rates were higher than WL patients if recipients had comorbidity.
Gill[94]	2013	US (USRDS) 1995-2007	25 468 potential recipients ≥65 y listed, 8373 received a DDKT (3348, 40% ECD)	Long-term survival advantage of KT recipients, even if ECD-KT compared with dialysis Higher early mortality risk = 130 to 521 d to equal survival if ECD-KT and 365 to 525 d if KDRI >1.51

Continued next page

TABLE 4. (Continued)

First author (reference)	Year published	Country, period	Number and demographics	Mortality risk
Massie[34]	2014	US (SRTR) 2002-2011	37 204 KDPI <70; 5213 KDPI 71-80; 4904 KDPI 81-90; 3389 KDPI 91-100	Better survival than remaining on dialysis with time to equal risk 1.7, 6, 7.2 mo for KDPI 71-80, 81-90, and 91-100
Lloveras[11]	2015	Spain 1990-2010	823 KT patients from donors ≥65 y compared to 823 counterparts on dialysis and listed matched by comorbidities	5 y PS 74.5% (KT) vs 44.2% (dialysis) Risk of death 2.66 higher for dialysis group
Pérez-Sáez[19]	2016	Spain 1990-2013	2040 potential recipients listed and who did not receive an organ <75 y, 389 received a KT patients from donors ≥75 y	Risk of mortality lower for transplant group HR 0.44 HR 0.17 if recipient ≤65 y; HR 0.56 if 65-69 y; HR 0.81 (NS) if ≥70 y Similar risk of mortality during the first year after transplant

AH, arterial hypertension; DM, diabetes mellitus; WL, waiting list.

confirmed that KT in advanced age patients is associated with prolonged graft survival, because patient survival is often the limiting survival factor for the kidney allograft.[17,27,28,48,50,103,104,106-108,110,112,114] Contrarily, some studies have shown higher mortality and worse death-censored graft survival in older recipients using ECD kidneys.[15,29,49,105,109,111] Although some studies showed similar survival using ECDs in younger recipients,[15,106] suboptimal results are frequently reported.[23,29,105,107,108,113-115]

VALUE OF PREIMPLANTATION BIOPSY AND OTHER ASSESSMENT TOOLS

One possibility to expand more confidently the use of old donor kidneys may be the assessment of preimplantation biopsies. Wang et al[116] performed recently a review on this topic, including a number of useful summarizing tables, concluding that routine use of biopsies to help determine whether or not to transplant a kidney should be reexamined. The reports published to date including a substantial number of biopsies, are of poor quality, heterogeneous and retrospective.[107,116-144] In agreement with Wang et al, we have been unable to pool the results in a meta-analysis, as all studies have reported results and outcomes in very different ways. A substantial number of reports conclude that the time-zero or preimplantation biopsy is of very limited value to predict outcomes, particularly renal graft function or survival.[117-128] It is likely that overestimation of glomerulosclerosis when the wedge biopsy is taken at a subcapsular level may mask the true importance of this parameter. SRTR reports including greater than 12 000 biopsies showed better 1-year graft function after transplanting kidneys with 0% to 5% glomerulosclerosis, compared with those showing higher percentages, but without any correlation with graft survival and loss of any discrimination power between 6% and 100% of sclerosed glomeruli.[122,123] Of particular importance is the Spanish study performed by Azancot et al, confirming the limited value of the preimplantation biopsy findings when assessed by the local on-call pathologist.[126] The histological parameters turned to be useful only when they were retrospectively re-assessed by an experienced renal pathologist, a resource unlikely available for most transplant programs. Some authors suggest that donor age correlates much better than histology with graft outcomes.[121]

Despite the negative results from the above mentioned studies, a good number of reports have underlined the value of time-zero or preimplantation biopsy in predicting outcomes.[107,129-144] Severity of histological findings inversely correlates with graft outcome, particularly glomerulosclerosis,[129,131,134] vascular disease and fibrous intimal thickening,[133,136] or a combination of vascular, interstitial and glomerular damage joined in different scores.[107,130,132,135-144] Remuzzi et al[132] suggested that better graft survival using ECD kidneys might be achieved if histological evaluation is performed before kidney allocation. The limitation of this study is that dual KT was the modality chosen for the majority of patients, and it is not unexpected to have good results by performing KT with 2 ECD kidneys with minimal fibrosis and vasculopathy.

Wang et al[116] have examined the value of 15 published semiquantitative scoring systems used to predict posttransplantation outcomes. Scores combining histological and clinical variables are of particular value.[107,130,134,139] The first such mixed score used data from the UNOS during the nineties to include 5 donor variables related to creatinine clearance at 6 months.[107] Six-year graft survival was 11% better in recipients scored greater than 20 versus those scored less than 20. In a further analysis, Nyberg score performed better to stratify survival than SCr at 2 to 4 years and ECD/non-ECD classification.[130] A French group optimized prediction of a low estimated GFR combining donor SCr, the presence or absence of donor hypertension and glomerulosclerosis greater than 10% or less than 10%.[134] The validation set in this study confirmed the weak prediction power of isolated clinical or histological parameters, which strongly improved in a combined composite score. De Vusser et al[139] prospectively studied baseline biopsies in 548 patients showing that interstitial fibrosis, tubular atrophy and glomerulosclerosis associated significantly with death-censored graft survival, whereas hialynosis and vascular thickening did not. In parallel, donor age correlated significantly with the same 3 predictive histological parameters, and also with graft survival. They constructed a new scoring system for prediction of 5-year graft survival that improved prediction of allograft loss with respect with previously published histological scores,[124,132,135] giving the strongest weight to donor age. Nonetheless, survival curves showed

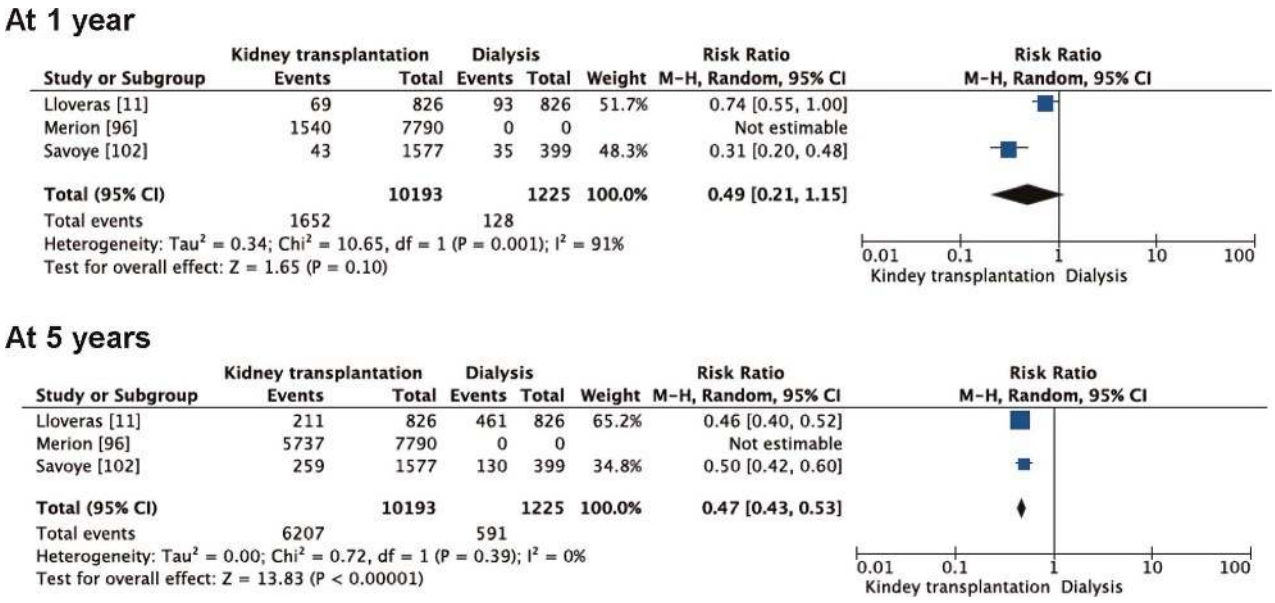


FIGURE 3. Comparison of mortality between patients undergoing kidney transplantation using ECDs and patients remaining on dialysis on the waiting list for kidney transplantation.

that those patients transplanted with a high scored kidney had around 80% graft survival al 5 years, and those getting a kidney with a low score had a great 90% 5-year graft survival. So in fact, the new score only confirmed that older kidneys had lower medium-term graft function and survival than younger kidneys, but not if they are worthy to be used or not.[139]

This literature overview confirms that preimplantation biopsy findings, in combination with other clinical and demographic donor characteristics may be useful to predict graft function in internal comparisons, but not to predict patient survival, graft survival or primary nonfunction. The extension of routine preimplantation biopsy has probably increased discard rate, which reaches 30% in biopsied kidneys versus 6.6% in not-biopsied ones, to the detriment of the large population in the waiting list for transplantation.[6] Only a good randomized clinical trial may resolve the usefulness of pretransplant biopsy for assessing the kidney graft quality and outcomes. Of course, all the biopsied kidneys might be transplanted in this hypothetical trial, to make sure absence of selection biases in outcomes. In our standard practice, biopsy findings are not anymore a tool to discard kidneys, but a tool to assess kidney graft prospects and baseline pretransplant damage, serving as a good self-control for posttransplant assessment.

DUAL KT

Dual KT has been proposed as a strategy to increase KT with suboptimal, particularly old, donor kidneys.[132] It is based in a prediction: the transplant physician considers that a single kidney from a given donor will not be sufficient to add sustained stable kidney function. Nonetheless, its practice is very limited, comprising only 2% to 4% of all KT performed in the US.[145,146] Although a common practice in some Spanish units in the past,[147-149] dual KT is very unusual nowadays in Spain, representing less than 1% of procedures. Most units prefer now transplanting a single kidney to optimize the kidney pool. Although some groups have tried to develop clinical algorithms to allocate single or dual KT according to donor renal function, histology and comorbidities, there is no uniform consensus.[132,146,150-152] In Figure 4, we have summarized the different applied strategies by several groups.

During the last decade, some centers have reported their experience performing dual KT without a comparison with a control group. Eight reports (n = 290) showed 1-year graft survival of 87% to 96%.[153-160] When outcomes are compared with those obtained after single KT with an ECD donor, many studies have reported similar patient and graft survival (**Table S5, SDC**, http://links.lww.com/TP/B387) [160–166,168,177-186]. We have been able to pool the results from 16 reports of dual KT in different outcomes.[145,146,148-150,152,161-170] The incidence of DGF was lower performing dual KT (n = 2564) versus single KT (n = 23812; RR, 0.81 [0.68-0.98]; $P = 0.03$). SCr at 1-year posttransplantation was similar after dual or single KT (9 studies; mean difference, –0.24 [–0.55 to –0.07]; $P = 0.13$). Graft loss at 1 year was similar between dual and single KT (9 studies, RR, 0.92 [0.73-1.15]; $P = 0.47$). However, in the pooled analyses including the 6 relatively small reports with graft loss at 5 years available, dual KT (n = 507) was associated with lower graft loss than single KT (n = 695) (RR, 0.45 [0.30-0.67]; $P < 0.0001$) (Figure 5). Mortality at 1 year was similar after dual (n = 1135) or single KT (n = 8583) (7 studies; RR, 0.94 [0.52-1.69], $P = 0.83$]. The largest study included patients from the US Registry allocated according to UNOS criteria into dual KT (n = 625), single ECD (n = 7686), and single SCD (n = 6044).[145] Mortality at 1 year was significantly higher after dual KT than after single KT (RR, 1.32 [1.02-1.71]), however, this difference disappeared when including the other 6 smaller studies. Mortality at 5 years was lower after dual KT (n = 443) versus single KT (n = 680) in the pooled analysis of 5 studies with this outcome available (RR, 0.61 [0.41-0.90]; $P = 0.01$) (Figure 5).

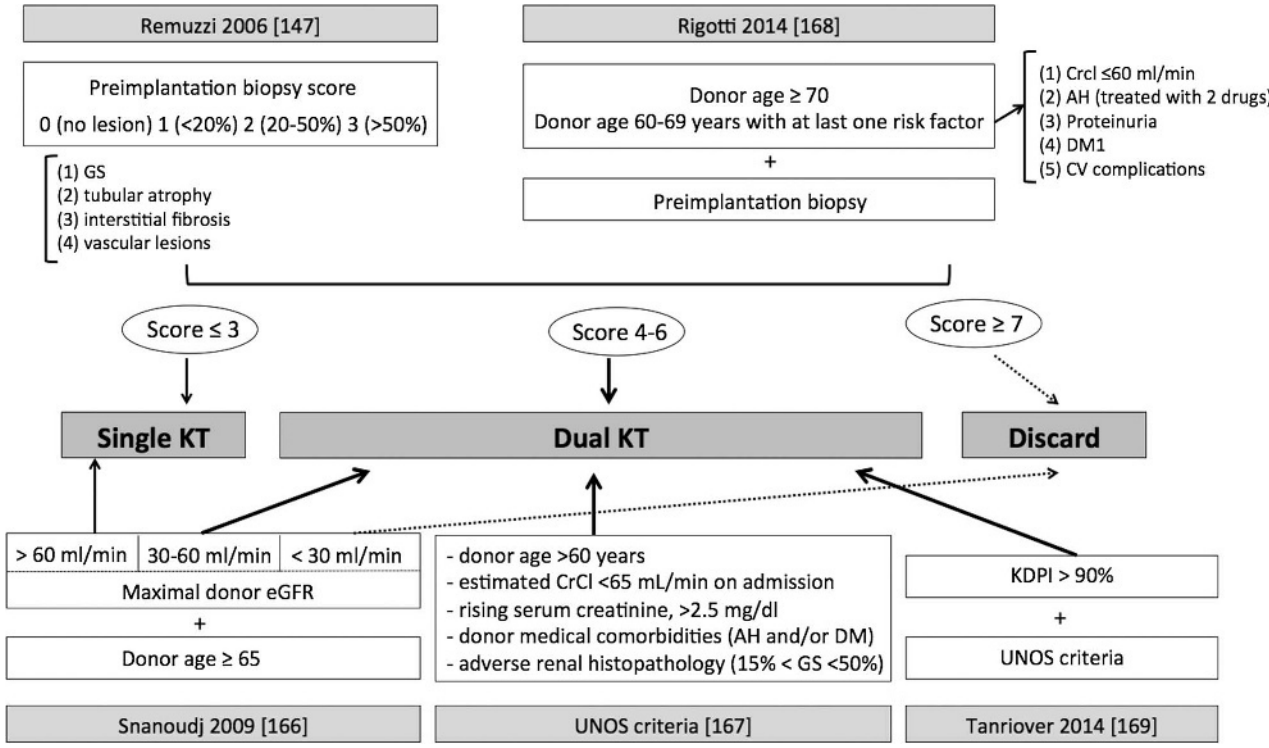


FIGURE 4. Different criteria for allocating kidneys to dual KT. According to Remuzzi et al,[132] the allocation of a dual KT may be based in histopathological criteria in preimplantation donor biopsy with the assessment of 4 compartments (glomerulosclerosis, tubular atrophy, interstitial fibrosis and vascular lesions). The score ascribes 0 to 3 points to each compartment according to the degree of lesions. If the overall score is 3 points or less, a single KT is carried out, between 4 and 6 points, a dual KT, and 7 points or more lead to kidney discard. Rigotti et al, in addition to the histological score, takes into account donor age and donor comorbidities.[152] If the donor is 70 years or older, or is 60 to 69 years old with at least 1 comorbid condition such as creatinine clearance below 61 mL/min, AH controlled with 2 drugs or more, proteinuria, diabetes or any cardiovascular complication, the recipient receives 2 kidneys in a dual KT. Snanoudj et al[150] proposal is based in donor kidney function and donor age: a donor 65 years or older and eGFR between 30 and 60 mL/min is allocated to dual KT, if >60 ml/min to a single KT and if <30 ml/min discarded.[150] UNOS criteria to allocate kidneys for dual KT are based in donor age (>60 years old), creatinine clearance (lower to 65 ml/min at admission), creeping creatinine after admission (to 2.5 mg/dl or higher) and comorbidities such as AH or DM, with glomerulosclerosis between 15-50%.[151] Tanriover proposal for dual KT is based in UNOS criteria for kidneys with a KDPI higher than 90%.[153] HTA, arterial hypertension; DM, diabetes mellitus; GS, glomerulosclerosis; eGFR, estimated glomerular filtration rate; CV, cardiovascular; CrCl, creatinine clearance.

More recently, Tanriover et al[146] performed an analysis based in the KDPI allocation system. The innovative approach, quite different than those previously published, precluded the inclusion of this important report in our pooled analysis. In the group of patients receiving kidneys with KDPI greater than 90%, dual KT was associated with slightly better 3-year death-censored graft survival than single ECD (72.9% vs 67.6%). Those differences disappear when the analysis is performed with the kidneys with KDPI greater than 80%.The authors propose to reserve dual KT for kidneys with KDPI greater than 90%.

The results of our pooled literature analyses underline a better patient and graft survival at 5 years in those patients receiving a dual KT than a single ECD KT. However, in our opinion, these differences are based in few reports with a relatively low number of cases, and the actual reported differences in survival are not enough to justify the investment of 2 kidneys in 1 recipient as a routine practice, given the shortage of organs and mortality rates in the waiting list.[6] But of course, given that 60% of kidneys from donors older than 65 years are currently discarded in the United States, their use in dual KT is better than full refusal. Better and larger studies would be needed to validate systematic selection of kidneys for dual KT, to optimize high KDPI/ECD organ use in those units with strict kidney selection criteria.

MACHINE PERFUSION WITH OLD KIDNEYS

Different studies have shown variable benefits of pulsatile machine perfusion to improve ECD kidney outcomes (Table 5).[171-184] Pulsatile perfusion has increased the rates of ECD use.[171,176] Recent meta-analysis showed reduced incidence of DGF and an increase in 1-year graft survival.[185,186] The analysis of the effect of machine perfusion in ECD from a randomized controlled trial found that the better graft survival was more relevant when DGF occurred.[176] Although this beneficial effect did not have significant impact in the 2- to 3-year patient survival rates,[174-182,185] the use of machine perfusion decreased economic expenses (taking into account direct costs such as dialysis, readmission and preservation costs) in the short and long-term.[186]

Some of the cited retrospective and prospective studies using hypothermic machine perfusion had available numerical data to perform a meta-analysis.[172-179,183,184] DGF rate is lower with machine perfusion (n = 13498) than with cold storage (n = 83342) (11 reports; RR, 0.71 [0.67-0.74]; $P < 0.00001$). Mortality at 1 year (3 studies;

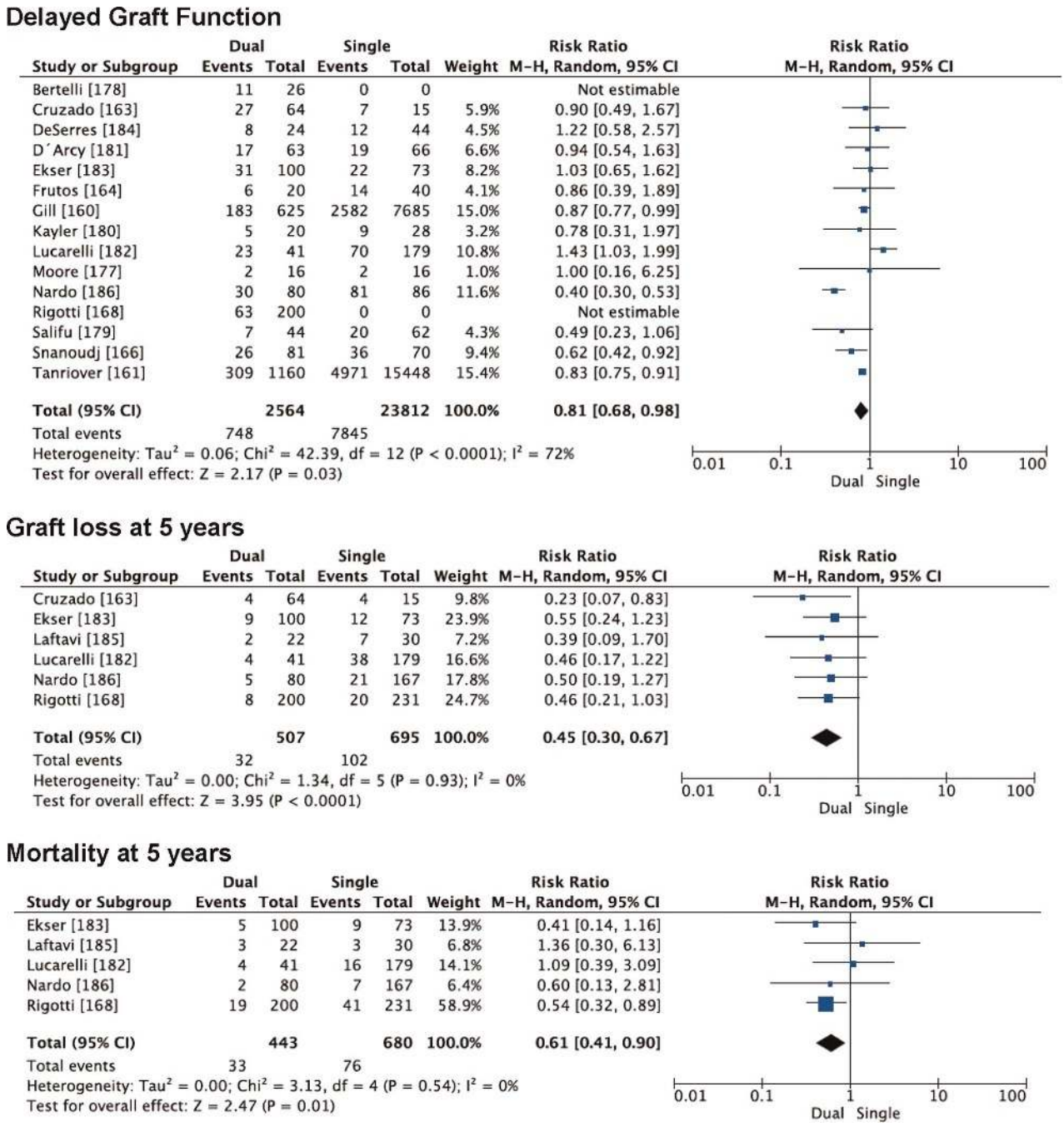


FIGURE 5. Outcomes after dual KT versus single transplantation using an ECD kidney.

RR, 1 [0.83-1.22]; *P* = 0.96] and 3 years (5 reports from 3 trials; RR, 0.94 [0.70-1.25], p = 0.66) and graft loss at 1 year (5 studies; RR, 0.87 [0.65-1.16]; *P* = 0.35) and 3 years (7 reports from 5 studies; RR, 0.98 [0.88-1.08]; *P* = 0.67) were not different using machine perfusion or cold storage. However, when we excluded retrospective registry articles and included only randomized clinical trials in our analyses,[175-179,183,184] DGF rate remains lower with machine perfusion (n = 300) than with cold storage (n = 207) (7 reports, RR 0.71 [0.51-1]; *P* = 0.05); mortality at 1 year (2 studies; RR, 1 [0.07-15-1.22], *P* = 0.1] was not different but graft loss at 1 year (3 studies, RR 0.43 [0.25-0.75], p = 0.003) and 3 years (3 reports from 2 studies; RR, 0.44 [0.26-75], *P* = 0.002) were lower using machine perfusion.

Evaluation of graft viability is especially important in advanced age, and machine perfusion could be a useful tool. However, the renal resistance at the end of machine perfusion was not a useful predictor for outcomes.[183,184]

Machine perfusion is used in a minority of KT from deceased donors, and the inconsistency of the potential benefits reported, in addition to concerns regarding cost-effectiveness factors, does not permit a generalized advise for its use to optimize old donor kidney outcomes. This is an area in which new large prospective randomized studies are clearly needed, as preservation technique improvement should be a very

TABLE 5.

Reports describing potential benefits of pulsatile perfusion machine use in kidneys from ECDs

Reference	Year published	Country/period	Patients/demographics		Benefits of PP		
			PP	No PP	ECD use	DGF	Survival
Schold[171]	2005	US (UNOS) 1994-2003	11 060	74 674	Increased (70% v 59%; OR, 1.71)	Lower rate (19.6% vs 27.6%)	Mildly better death-censored GS with PP
Matsuoka[172]	2006	US (UNOS) 2000-2003	910	3708	—	Lower rate (26% vs 37%)	Similar 3-y GS
Stratta[173]	2007	US 2001-2006	114	27	—	Lower rate (11% vs 37%)	Similar GS (81% vs 81.5%) and PS (91% vs 96%) after 27 mo
Buchanan[174]	2008	US (USRDS) 1995-2004	1114	4726	—	Lower rate (26.9% vs 38%, $P < 0.0001$)	Similar GS (HR, 0.97; 95% CI, 0.86-1.08) and PS (HR, 0.99; 95% CI, 0.87-1.13)
Abboud[175]	2011	France 2007-2009	22	22	—	Lower rate (9% vs 31.8%, $P = 0.02$)	Same PS (95.5% both) and similar GS (95.5% vs 90.9%)
Treckmann[176]	2011	Germany 2005-2006	91	91	45.5% of potential donors were used	Lower rate (22% vs 29.7%, $P = 0.27$)	Similar GS (92.3% vs 96.7%, $P = 0.30$) Similar PS (93.4% vs 96.7%, $P = 0.30$)
MP trial Moers[177,178] Gallinat[179] Jochmans[180]	2013	Eurotransplant 2005-2009	94	94	—	Lower rate (23% vs 31%, $P = 0.42$)	Better GS (86% v 76%; adjusted HR, 0.38; $P = 0.01$) at 3 y
Nicholson[181]	2013	UK 2010-2012	18 normothermic perfusion (32-36°) using a red cell-based plasma-free solution	47	—	Lower rate (5.6% vs 36.2%, $P = 0.014$)	No differences in 1-y GS (100% vs 98%, $P = 0.5$) or PS (100% vs 92%)
Gill[182]	2014	Canada 2000-2011	5804	9318	—	Lower risk 0.59 (0.53-0.66)	—
Gómez[183] Burgos Revilla[184]	2015	Spain 2012-2014	93	—	100%	14.3% (no comparator)	PS, 89.5% (in historical ECD series 81%) at 1 y

PP, pulsatile perfusion.

relevant strategy to expand the use of advanced age kidneys and other damaged organs.

IMMUNOSUPPRESSIVE STRATEGIES FOR BETTER USE OF OLD KIDNEYS

Elderly recipients of an old renal graft are a special population with increased risk of poor graft function, calcineurin inhibitor (CNI)-induced nephrotoxicity, infections, cardiovascular events and malignancies. Amplification of senescence changes of the kidney allograft exaggerates the negative impact of acute rejection episodes.[14,187] As a result, it is important to maintain adequate immunosuppression with a tailored drug regimen.

Our review confirms that the scarcity of immunosuppressive strategies especially designed for the elderly recipient receiving an old kidney. We have focused this review on the studies published along the last 10 years (Table S6, SDC, http://links.lww.com/TP/B387)[204–223], as the previous ones had already been reviewed.[14] The great heterogeneity of the studies and the absence of many numerical outcomes in the different reports, precluded any meaningful pooled meta-analysis.

CNIs are nephrotoxic and 2 possible strategies have been proposed for CNI toxicity minimization: (1) to delay introduction until a certain level of renal graft function is achieved, and (2) more radical, complete CNI-free strategies. Delayed introduction has been analyzed in 3 European studies, all of them with induction with anti–interleukin-2-receptor antibodies (anti-IL2ra).[188-190] Reduced CsA doses (3 mg/kg/d) initiated within the first 24 hours posttransplantation with mofetil mycophenolate (MMF), basiliximab and steroids, were not associated with an increased risk of acute rejection.[188] A delayed initiation of cyclosporine after 7 days posttransplantation did not show any benefit in DGF prevention and increased acute rejection rates (25% vs 5.3%). Two

controlled studies evaluating delayed-initiation of tacrolimus showed similar renal function and patient and graft survival at 6 months in delayed and immediate tacrolimus groups.[189,190]

Regarding CNI-free initial immunosuppression, a combined induction using antithymocyte globulin (ATG) and basiliximab using only MMF for low-risk allograft recipients brought high incidence of acute rejection and cytomegalovirus infections.[191,192] When the elderly population was compared to the younger, there was a high risk of rejection because of a larger mismatch. Durrbach et al[193] compared a strategy with early introduction of sirolimus vs CNI-based immunosuppression describing a higher incidence and longer duration of DGF, with lower graft survival in sirolimus patients. The comparison of CNI-MMF-steroids versus sirolimus-MMF-steroids using antibody-based induction therapy reported no differences between both groups.[194] CNI-free treatment regimen using MMF plus a mammalian target of rapamycin inhibitor showed no difference in acute rejection with the CNI-treated patients, but a high incidence of switching to CNI in the initial CNI-free group.[195]

Old kidneys are generally transplanted in elderly recipients, so it seems reasonable to minimize induction therapy to prevent adverse effects in this vulnerable population. Old-for-old strategies, usually results in poor HLA matching, thus encouraging physicians to use induction therapy.[29] Seven studies have compared different induction strategies in this population. A lower risk of DGF using ATG than anti-IL2ra and a higher risk of acute rejection with anti-IL2ra than using ATG or alemtuzumab is observed.[196] Despite this apparent advantage of depletive induction agents, a greater 1-year mortality with alemtuzumab than ATG was described in KT using kidneys from ECD, DCD or with prolonged cold ischemia time. Two studies showed that ATG showed better acute rejection prevention than basiliximab, without differences in DGF or survival.[197,198] However, higher acute rejection rates and lower survival were observed with a protocol of ATG in elderly recipients. Cumulative ATG dosage >6 mg/kg was associated with death with functioning graft, and the authors advise against high ATG dose in the elderly.[199] These negative results were not confirmed in a similar study.[200]

A different strategy is the use of belatacept. Low-intense belatacept-based regimen was associated with better renal function compared to a cyclosporine-based regimen,[201-206] with a better control of cardiovascular risk factors.[204] A greater risk for posttransplant lymphoproliferative disease was observed in patients negative for Epstein-Barr virus at baseline and were treated with a belatacept-based regimen.[201]

The immunosuppressive drug protocol for KT using old kidneys should be based on potential nephron-protecting strategies.[207] These include a tailored immunosuppression with early CNI minimization or delayed moderate dose CNI addition after induction, and adequate infection prophylaxis.

CONCLUSIONS: USE THESE KIDNEYS

Relying in donors with associated comorbidities and/or an advanced age is unavoidable to overcome the increasing waiting lists. Despite poorer results, the use of old kidneys targeted to a selected population may provide better survival than remaining on dialysis. The use of advanced age DCD kidneys is associated with outcomes not different to those seen with kidneys from ECD after brain dead. Preimplantation biopsy assessment has been overestimated for kidney graft discarding or use. Machine perfusion has decreased DGF and this beneficial effect has resulted in better graft survival in medium-size trials that should be confirmed in larger ones including advanced age kidneys. Investing 2 kidneys in 1 recipient does not make sense when a single KT would be enough, particularly in many elderly recipients. In these recipients, randomized trials with adapted immunosuppression strategies are urgently needed.

Old donors constitute an enormous potential source of useful kidneys, but their use in a vast majority of countries is limited. Strategies and policies should be fostered to solve it.

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