Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Kidney Transplantation Following Cardiocirculatory Death: A Review of the Clinical Evidence and Guidelines

DATE: 3 December 2013

CONTEXT AND POLICY ISSUES

According to the Canadian Institute for Health Information (CIHI), 3,404 Canadians were on a waiting list to receive an organ for transplant in 2012.[1] Kidneys represented nearly two thirds of the organs needed for transplantation in this country. In 2012 alone, there were 2,450 patients (active and on hold) on the waiting list for a kidney. Fifty-nine of these patients died while waiting for a transplant.[1]

Traditionally, organs for donation have come from either from living donors or donors who experienced brain death. These organs can be procured from the donor while the heart is still beating and blood is flowing through the body.[2] The number of organs available from these donors has never been sufficient to provide for all of the patients on the waiting lists for transplant. More recently, donation after cardiocirculatory death (DCD) has been investigated as a method to increase the number of organs available for donation. A report covering the first 25 years of transplantation in Maastrict, Netherlands showed a 44% increase in overall organ donation when DCD was allowed.[3] In 2012, 1,025 total adult kidney transplants were performed in Canada.[1] Of these, only 111 kidneys were DCD and 504 donation after brain death (DBD). Of 1533 retrieved organs, 183 were from DCD donors. The practice of DCD began in Canada in 2006 and the number of donors has increased from four in the first year to 71 in 2012.[1]

In Canada and the US, controlled DCD is most commonly used method.[4] Controlled cardiac death occurs in-hospital after it has been decided that life-sustaining therapy should be withdrawn and resuscitation not performed. The medical staff waits until after two to five minutes of demonstrated mechanical asystole before declaring death and procuring organs for transplant. In contrast, uncontrolled DCD includes donation from patients who have died outside of the hospital, were unsuccessfully resuscitated, or critically ill patients who experienced unexpected cardiac arrest in the hospital.[2]

Policy makers require information on the relative benefits and risks associated with the donation of kidneys following cardiocirculatory death in order to support clinical practice decisions. The objective of this review is to evaluate the clinical evidence regarding the outcomes of patients who receive kidneys via DCD and the guidelines for the retrieval of kidneys from patients who experience cardiocirculatory death.

RESEARCH QUESTIONS

1. What is the clinical evidence regarding the outcomes of patients who receive kidney transplants from a donor who experienced cardiocirculatory death as compared with kidney transplants from a donor who experienced brain death?

2. What are the evidence-based guidelines regarding the retrieval of kidneys for donation from patients who experienced cardiocirculatory death?

KEY FINDINGS

The evidence suggests that medium-term patient and graft survival are similar between groups receiving kidney transplants from donations following cardiocirculatory death and from donations following brain death, despite a higher incidence of delayed graft function following donation after cardiocirculatory death. These findings should be viewed with caution given the study limitations including the retrospective observational study design, residual confounding, limited sample size and lack of statistical power to detect differences between groups.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and November 6, 2013.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults requiring kidney transplant
Intervention	Kidney procurement/transplantation following cardiocirculatory death (DCD)
Comparator	Kidney procurement/transplantation following neurologic (brain) death (DBD)
Outcomes	Clinical effectiveness, outcomes of recipient patients, guidelines and best practice for procurement
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008.

Critical Appraisal of Individual Studies

The included non-randomized studies were critically appraised using the Downs and Black instrument.[5] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 526 citations were identified in the literature search. Following screening of titles and abstracts, 502 citations were excluded and 24 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 15 publications were excluded for various reasons, while nine non-randomized studies met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of study design, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

Study Design

The nine included studies were retrospective cohort studies.[3,6-13] All studies compared the outcomes of patients receiving kidneys from DCD with patients receiving kidneys from DBD. One study included all patients on the transplant wait list and compared those remaining on dialysis with those who received kidneys from DCD or DBD.[13]

Five studies took place in a single centre.[6,9-12] Two studies involved multiple centres[3,8] and two studies used transplant registries to obtain their data.[8,13] One study did not clearly define how

many centres were involved.[7] The studies included up to 29 years of transplant data and included patients who received kidney transplants between 1980 and 2010.

Country of Origin

Four studies took place in the UK,[6-9] three studies were from the USA,[10-12] and two studies focused on the Netherlands.[3,13]

Patient Population

Four studies included organs procured from donors who experienced controlled cardiac death,[6,8,11,12] four studies included organs procured from donors who experienced controlled and uncontrolled cardiac death,[3,9,9,13] and the ninth study did not clearly describe the way the donors died.[7] Fewer patients received a kidney transplant from DCD (study median = 113 [range 64 to 1038]) than from DBD (median = 508 [range 164 to 8,289]).

Clinical Outcomes

The most commonly reported clinical outcomes were patient survival,[3,6,7,9-13] delayed graft function,[3,6-12] graft survival,[6-12] acute rejection,[6-9,11,12,12] primary non-function,[3,6,7,9] and death-censored graft survival.[3,6,9,10,12]

Summary of Critical Appraisal

The strengths and limitations of included studies are summarized in Appendix 3.

The aim, objective, interventions, and main outcomes of the studies were all clearly described. Patient characteristics and baseline differences between groups were clearly presented in all studies, except Singh et al.[12] The main study findings were clearly presented and the main outcomes reported were similar among all studies. Statistical methods were clearly described.[3,6-13]

In general, the included studies were limited by their retrospective and observational design.[3,6-13] Although differences in patient characteristics were noted between groups, six studies attempted to control for potential confounders through matching[3,7,9] or conducting adjusted analyses.[3,8,10,13] The authors of three studies[6,10,12] indicated that the sizes of the samples may have been too small to adequately power their analyses. No power calculations were provided in any of the included studies. Methods for dealing with missing data and patients lost to follow up were not described in five studies.[6,7,10,11,13] Wadei et al.[10] indicated that visual inspection of organs prior to transplantation could have introduced selection bias and reduced the generalizability of their findings. Snoeijs et al.[13] suggested their study might also have been subject to selection bias because patients receiving a transplant would likely be healthier than those remaining on dialysis. This difference may have skewed their results comparing the transplant to dialysis population but not the comparison between DCD and DBD recipients. The generalizability of the results from Barlow et al.[9] might be limited due to the strict inclusion criteria that were applied to their patient population.

Summary of Findings

What is the clinical evidence regarding the outcomes of patients who receive kidney transplants from a donor who experienced cardiocirculatory death as compared with kidney transplants from a donor who experienced brain death?

A summary of study findings is provided in Appendix 4.

Delayed graft function, which is indicated by the need for dialysis within the first week following transplant, was statistically significantly more common in recipients of kidneys from DCD than from DBD in all eight studies reporting this outcome.[3,6-12] The proportion of patients with delayed graft function ranged from 30% to 84% for the DCD recipients, and from 16% to 28% for the DBD recipients.[6-9,11,12]

Primary non-function refers to a graft that does not function well enough to allow the patient to cease dialysis.[9,12] Primary non-function rates were not significantly different between groups in two studies,[6,9] and were significantly higher in the DCD group than the DBD group in one study.[7] In a fourth study, after adjusting for confounders, the odds of primary non-function were statistically significantly higher for DCD kidneys as compared to DBD kidneys (odds ratio [OR] 7.51; 95% confidence interval [CI], 4.01 to 14.1; $P < 0.001$).[3]

The incidence of acute rejection was reported in seven studies,[6-12] and all but one[8] stated that rejection was verified through biopsy. Two studies found that acute rejection occurred in significantly fewer DCD recipients,[6,8] while one study found significantly higher rates of acute rejection in the DCD than the DBD group.[12] Three studies did not identify a significant difference in biopsy-proven acute rejection between groups.[7,9,10] Bellingham et al.'s study[11] found the occurrence of acute rejection was statistically significantly lower among DCD recipients than DBD recipients who received transplants between 1980 and 1992, but the differences between groups were no longer significantly different for those receiving transplants between 1993 and 2008.

Graft loss was defined as removal of a transplanted kidney, return to dialysis therapy, or re-transplantation in three studies,[3,8,13] and in a fourth study,[12] the criteria also included a return to pre-transplant serum creatinine levels. Five studies did not define graft loss.[6,7,9-11] Graft survival is usually measured as the time from transplant to graft loss, death, or the end of follow up (censored), whichever comes first. For death-censored graft survival, patients who die with a functioning graft are censored (treated as a case lost to follow up, not as a graft failure). This analysis assumes that deaths were not related to the transplant. In the analysis of all-cause graft survival, patients who die with a functioning graft are considered to be graft failures, and the analysis gives an overall rate of success in terms of graft and patient survival. Patient survival was measured as the time from transplant to death or the end of follow-up, whichever comes first.

There was no significant difference in graft survival found between recipients of DCD or DBD kidney transplants in six studies,[6,7,10,12] including first time transplant recipients.[8,9] Graft survival rates at one and three years,[7] four years,[6] five years,[8] and up to 15 years,[9] were not significantly different between groups. One study (Snoejis et al.[13]), found graft failure in the first three months was twice as likely for patients receiving DCD kidneys (12% vs 6%, $P = 0.001$). Bellingham et al.[11] examined the outcomes of transplant recipients in two time periods – 1980 to 1992 and 1993 to 2008. Between 1980 and 1992, graft survival rates were significantly lower in

the DCD group than the DBD group (*P* = 0.04) but no significant difference was found among those who received transplants between 1993 and 2008.[11]

In three studies there was no significant difference between groups in death-censored graft survival up to 15 years[6,9,12] but, in a fourth study, DCD was associated with an increased risk of death-censored graft loss at 15 years (HR 1.82; 95% CI, 1.37 to 2.42; *P* <0.001).[3] Wadei et al.[10] found no difference in the composite primary endpoint (death-censored graft loss or two consecutive iothalamate glomular filtration rate measurements of <50mL/min), between those who received DCD or DBD transplants.

Six studies found no statistically significant differences between groups in patient survival in up to 15 years of follow up.[3,6,7,10-12] In one study, standard criteria DCD transplant was associated with a 56% reduced risk (HR 0.44; 95% CI, 0.24 to 0.80; *P* = 0.007) for mortality as compared to conventional therapy (defined as dialysis treatment or waiting on dialysis until standard criteria DBD transplantation).[13] However, those who received extended criteria DCD (defined as a donor ≥60 years, or between 50 and 60 years with two additional risk factors), showed no statistically significant reduction in mortality compared to conventional therapy (HR 0.61; 95% CI, 0.31 to 1.19; *P* = 0.15).[13]

What are the evidence-based guidelines regarding the retrieval of kidneys for donation from patients who experienced cardiocirculatory death?

No relevant evidence-based guidelines were identified from the literature search results. Three clinical practice guidelines[14-16] that did not meet our criteria to be considered evidence-based were identified and references are provided in Appendix 5.

Limitations

The included studies were retrospective cohort in design. It was not clear how the investigators dealt with missing data or patients lost to follow up in five of the included studies.[6,7,10,11,13] There were no calculations provided to indicate whether the studies were statistically powered to detect a difference in recipient outcomes between DCD and DBD. Subjects were chosen from existing data resource from the US, UK and Netherlands, and it is unclear whether these existing sources of data provide a patient population that is representative of the Canadian transplant population. Although attempts were made in six studies to control for between-group differences in prognostic factors, residual confounding is likely. Changes in surgical and immunosuppressive treatments over time may have affected the outcomes for recipients of DCD relative to DBD transplants.

No relevant evidence-based guidelines were identified from the literature search results.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This report aimed to review the evidence regarding the clinical outcomes for recipients of kidney transplants from donation after cardiocirculatory death (DCD) as compared with kidney transplants from donation after brain death (DBD). Nine relevant non-randomized studies were identified. The evidence suggests that medium-term patient and graft survival are similar between DCD and DBD groups, despite a higher incidence of delayed graft function associated

with DCD. It is unclear whether there is a difference in primary non-function or acute rejection between DCD and DBD recipients.

These findings should be viewed with caution given the limitations of the studies such as the retrospective observational study design, residual confounding, limited sample size, and lack of statistical power to detect differences. Given that this report is focused only on the kidney, further research is required to determine the suitability of DCD for other organs.

No evidenced-based guidelines were identified for patients undergoing kidney transplantation.

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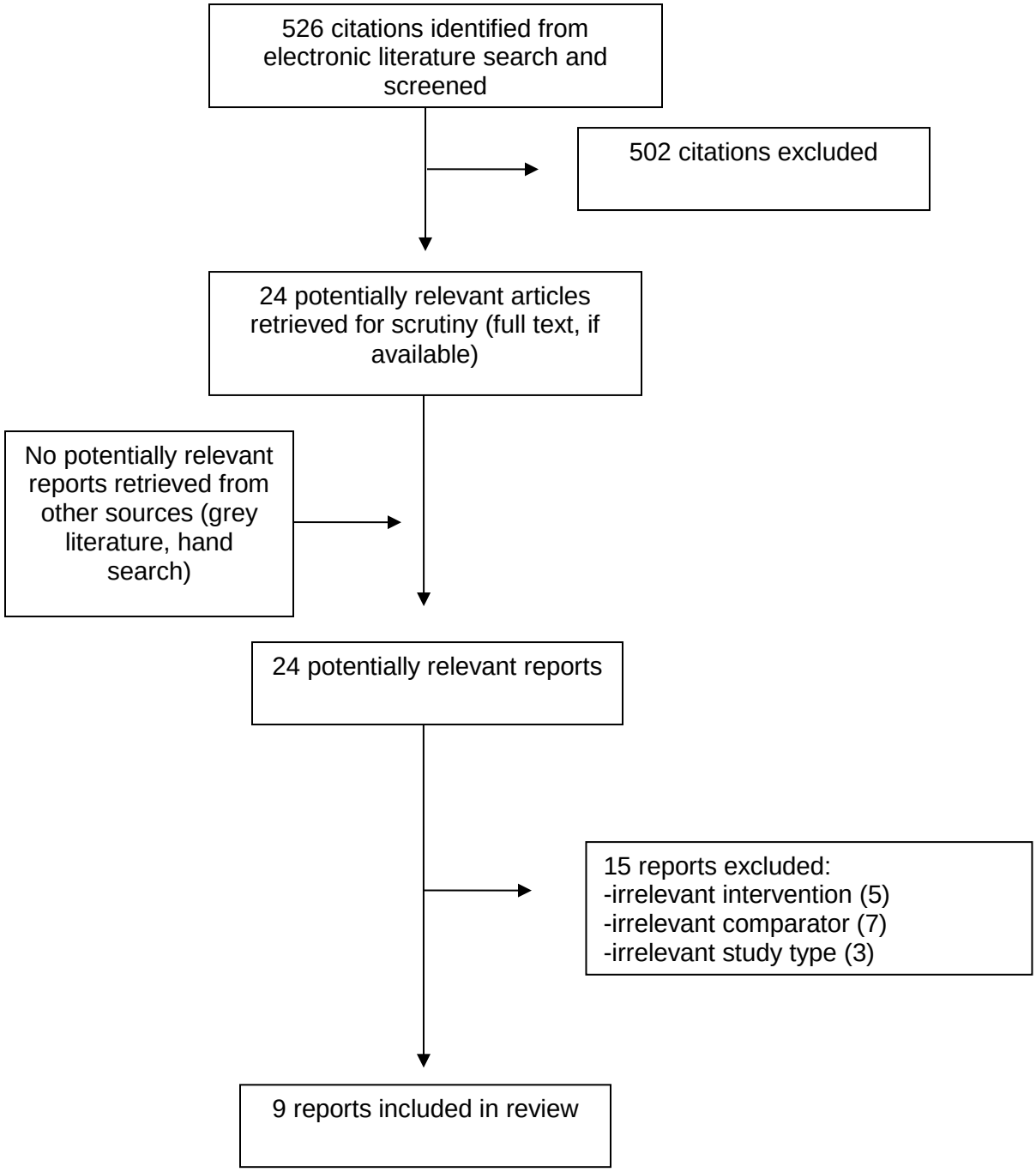
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Study Characteristics

Primary Author, Year, Country, Study Type, (transplant years)	Objectives, follow up	Recipient Characteristics (%)	Clinical Outcomes Measured
Wadei[10] 2013 USA Retrospective chart review (2000-2008)	To compare kidney function between DCD and DBD kidney transplant recipients	**DCD** n = 64 mean age = 56 years (range 25 to 79) male = 40 (63) white = 37 (58) **DBD** n = 248 mean age = 57 years (range 21 to 83) male = 141 (57) white = 157 (63)	**Primary endpoint** Composite of death-censored graft loss or two consecutive iGFR < 50mL/min/1.73m^2 occurring within 5 years of transplant **Secondary endpoints** Death Graft loss or death
Nagaraja[6] 2012 UK Single-centre retrospective cohort study (2004-2010)	To compare medium-term graft and patient outcomes between controlled DCD and DBD kidney transplants. Median follow up = 4.5 years	**DCD** n = 80 Median age = 51.5 years (range 19 to 72) Male = 54 (68) **DBD** n = 226 Median age = 51 years (18 to 78) Male = 144 (64)	**1 year** Graft survival rate Patient survival rate eGFR serum creatinine biopsy-proven acute rejection **4 year** Death-censored graft survival
Bellingham[11] 2011 USA Retrospective review (1980-2008)	To report the long-term outcomes of organs transplanted after controlled DCD	**DCD** n = 1038 Mean age = 44.8 years (SD = 13.2) Male = 587 (57) **DBD** n = 3470 Mean age = 47.6 years (SD = 13.4) Male = 1606 (46)	patient survival graft survival DGF acute rejection
Pine[7] 2010 UK Case-matched retrospective	To compare initial DCD experience with DBD results	**DCD** n = 103 Mean age = 50.4 years Male = 60 (58) **DBD** n = 183	Delayed graft function Primary non-function Biopsy-proven acute rejection episodes eGFR Recipient survival at 1 and 3 years

cohort study (2002-2007)		Mean age = 50.5 years Male = 104 (57)	Graft survival at 1 and 3 years
Singh[12] 2011 USA Single centre retrospective chart review (2001-2008)	To evaluate the impact of delayed graft function on controlled DCD transplant outcomes. Mean follow-up 36 months	Overall recipient characteristics were not described **DCD** n = 70 **DBD** n = 508	Patient death Death-censored graft loss Biopsy-proven acute rejection episodes Infections Renal allograft function
Snoeijs[3] 2010 Netherlands Case-matched retrospective cohort (1981-2005)	To report the first 25 years of DCD kidney transplants. Recipients of controlled and uncontrolled DCD kidneys with matched DBD controls. Mean follow up: ~ 6.8 years	**DCD** n = 297 mean age = 49 years (SD = 13) male = 66 (34) **DBD** n = 594 mean age = 49 years (SD = 13) male = 57 (43)	**All grafts** Primary non-function Death-censored graft survival at 15 years Patient survival at 15 years **Viable Grafts** Delayed graft function Duration of delayed graft function GFR at 1 year Decline in GFR Death-censored graft survival at 15 years Patient survival at 15 years
Snoejis[13] 2010 Netherlands Retrospective cohort study (1999-2005)	To determine the survival advantage of kidney transplant from controlled or uncontrolled DCD over remaining on dialysis and waiting for DBD transplant. Mean follow up (years): DCD 1.7, DBD 2.3, Dialysis 1.8	**DCD** n = 459 Mean age = 51 years (SD = 13) Male = 63% **DBD** n = 680 Mean age = 46 years (SD = 18) Male = 57% **Waiting list** n = 2575 Mean age = 49 years (SD = 15) Male = 60%	Overall mortality of DCD or DBD compared with waiting on dialysis Graft failure
Summers[8] 2010 UK	To compare outcomes following kidney transplant after controlled DCD	**DCD** n = 845 mean age = 49.3 years (SD = 12.8) male = 542 (64)	Primary non-function Graft failure up to 30 days Immediate function Acute rejection up to 3 months

Multi-centre retrospective cohort study (2000-2007)	or DBD and to identify factors that affect graft survival and function Median follow-up 6.1 years	white = 695 (83) **DBD** n = 8289 mean age = 46.8 years (SD = 13.0) male = 5065 (61) white = 6925 (85)	eGFR (mL/min/1.73m^2) Sensitization at transplantation Graft survival up to 5 years Survival of patients up to 5 years
Barlow[9] 2009 UK Case-matched retrospective cohort study (1992-2003)	To provide data on the long-term graft survival and function of renal transplants from NHBD compared with HBD donors (controlled and uncontrolled) Follow up = 5 to 15 years	**NHBD** n = 112 mean age = 49 years (SD = 12) male = 72 (64.3) **HBD** n = 164 mean age = 48 years (SD = 13) male = 105 (64.0)	Primary non-function DGF early death immediate graft function

DBD = donation after brain death; DCD = donation after cardiac death; DGF = delayed graft function; eGFR = estimated glomerular filtration rate; HBD = heart beating donors; iGFR = iothalamate glomerular filtration rates; NHBD = non-heart beating donors; SD = standard deviation; UK = United Kingdom

APPENDIX 3: Summary of Critical Appraisal

Downs and Black[5]	
Strengths	**Limitations**
Wadei[10] 2013	
• aim, objective, interventions, patient characteristics, main outcomes, and findings of the study are clearly described • controls were chosen from the same centre as intervention group • statistical methods are clearly described and *P* <0.05 was considered to be significant • analysis was adjusted for potential confounders	• patient selection criteria were not clearly described • no blinding of patients, investigators, or assessors due to the retrospective nature of the study • methods for dealing with missing data and patients lost to follow up were not described • the authors suggest the sample size was too small to adequately power the analyses and results should be considered as exploratory • visual inspection of organs prior to transplantation could have introduced selection bias and reduced generalizability of the findings • no power calculation
Nagaraja[6] 2012	
• aim, objective, interventions, patient characteristics, main outcomes, and findings of the study are clearly described • cases and controls were chosen from a single centre • statistical methods are clearly described and *P* <0.05 was considered to be significant	• no blinding of patients, investigators, or assessors due to the retrospective nature of the study • methods for dealing with missing data and patients lost to follow up were not described • the authors indicated their analysis may have been underpowered to detect differences in outcomes in DCD recipients with and without DGF • no power calculation • analyses were not adjusted for potential confounders and differed in the proportion undergoing first transplant and HLA mismatches
Bellingham[11] 2011	
• aim, objective, interventions, main outcomes, and findings of the study are clearly described • study population included all patients receiving DCD or DBD kidney transplant in a time period from one centre • statistical methods are clearly described and *P* <0.05 was considered to be significant	• patient characteristics and baseline differences between groups were not clearly described • no blinding of patients, investigators, or assessors due to the retrospective nature of the study • methods for dealing with missing data and patients lost to follow up were not described • no power calculation • analysis was not adjusted for potential confounders
Pine[7] 2010	

• aim, objective, interventions, patient characteristics, main outcomes, and findings of the study are clearly described • cases and controls were chosen a single centre • statistical methods are clearly described and *P* <0.05 was considered to be significant	• no blinding of patients, investigators, or assessors due to the retrospective nature of the study • methods for dealing with missing data and patients lost to follow up were not described • no power calculation • no adjustment of potential confounders however patients were matched on several variables
Singh[12] 2011	
• aim, objective, interventions, main outcomes, and findings of the study are clearly described • all consecutive transplant patients from a single centre were included	• patient characteristics at baseline were not reported • no blinding of patients, investigators, or assessors due to the retrospective nature of the study • small number of subjects in the DCD group may have limited the analysis • no power calculation • analysis was not adjusted for potential confounders • reporting of statistical analysis was unclear, thus it is difficult to determine if methods used were appropriate.
Snoeijs[3] 2010	
• aim, objective, interventions, patient characteristics, main outcomes, and findings of the study are clearly described • cases and controls were chosen from one procurement program • methods for dealing with missing data and patients lost to follow up were described • statistical methods are clearly described and *P* <0.05 was considered to be significant • multivariable regression was used to adjust for potential confounders	• no blinding of patients, investigators, or assessors due to the retrospective nature of the study • no power calculation
Snoejis[13] 2010	
• aim, objective, interventions, patient characteristics, main outcomes, and findings of the study are clearly described • included all patients on the Dutch waiting list for first transplant and dialysis patients from Renine database • statistical methods are clearly described and *P* <0.05 was considered to be significant • multivariable regression was used to	• no blinding of patients, investigators, or assessors due to the retrospective nature of the study • may be subject to selection bias – patients receiving transplant will likely be healthier than those remaining on dialysis • methods for dealing with missing data and patients lost to follow up were not described • no power calculation

adjust for potential confounders	
Summers[8] 2010	
• aim, objective, interventions, patient characteristics, main outcomes, and findings of the study are clearly described • cases and controls were chosen from the same data registry and inclusion criteria are described • statistical methods are clearly described and *P* <0.05 was considered to be significant • patients with missing data were dropped from the analysis • graft survival analysis adjusted to account for confounders; all other outcomes were unadjusted for differences in baseline characteristics present	• no blinding of patients, investigators, or assessors due to the retrospective nature of the study • no power calculation
Barlow[9] 2009	
• aim, objective, interventions, patient characteristics, main outcomes, and findings of the study are clearly described • controls were chosen from the same centre as intervention group • bias from potential confounders known to impact transplant outcome were minimized through matching criteria for case and controls • methods for dealing with missing data and patients lost to follow up were described • statistical methods are clearly described and *P* <0.05 was considered to be significant	• no blinding of patients, investigators, or assessors due to the retrospective nature of the study • generalizability is limited due to the strict inclusion criteria • no power calculation

DBD = donation after brain death; DCD = donation after cardiocirculatory death; DGF = delayed graft function

APPENDIX 4: Main Study Findings

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings</th></tr>
<tr><td>Wadei[10]
2013</td><td>DCD (n = 64) vs DBD (n = 248)
adjusted analysis (covariates not specified)

Delayed graft function
RR 1.66; 95% CI, 1.02 to 2.71; P = 0.041

Biopsy proven rejection
RR 1.32; 95% CI, 0.71 to 2.45; P = 0.39

Death-censored graft loss or two consecutive iGFRs<50
RR 1.16; 95% CI, 0.68 to 1.97; P = 0.59

Graft loss or death
RR 1.09; 95% CI, 0.58 to 2.06; P = 0.79

Death
RR 0.97; 95% CI, 0.41 to 2.27; P = 0.94</td></tr>
<tr><td>Nagaraja[6]
2012</td><td>All recipients [DCD (n = 80) vs DBD (n = 226)] (unadjusted analysis)

Delayed graft function
73% vs 27%; P <0.001
Primary non-function
1 (1.3%) vs, 5 (2.2%), p=0.6

Biopsy proven acute rejection
9% vs 23%; P <0.001

1 year/4 year graft survival
94% vs 90% / 79% vs 82% P = 0.44

4 year death-censored graft survival
95% vs 91%; P = 0.26

Patient survival
No significant difference between groups, P = 0.9</td></tr>
<tr><td>Bellingham[11]
2011</td><td>DCD (n = 965) vs DBD (n = 2674) (unadjusted analysis)

delayed graft function
35.7% vs 20.3%; P ≤ 0.0001

<table>
<tr><td>Era</td><td colspan="2">1980-1992</td><td colspan="2">1993-2008</td></tr>
<tr><td></td><td>DCD</td><td>DBD</td><td>DCD</td><td>DBD</td></tr>
<tr><td colspan="5">Delayed graft function (%)</td></tr>
<tr><td></td><td>30</td><td>16</td><td>45</td><td>22</td></tr>
<tr><td colspan="5">Free of acute cellular rejection (%)*</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td>1 year</td><td>33</td><td>50</td><td>70</td><td>66</td></tr>
<tr><td>3 year</td><td>30</td><td>46</td><td>67</td><td>61</td></tr>
<tr><td>10 year</td><td>26</td><td>41</td><td>58</td><td>55</td></tr>
<tr><td>P value</td><td colspan="2">≤0.001</td><td colspan="2">0.07</td></tr>
<tr><td colspan="5">Graft survival (%)</td></tr>
<tr><td>1 year</td><td>72</td><td>83</td><td>87</td><td>89</td></tr>
<tr><td>3 year</td><td>63</td><td>74</td><td>77</td><td>78</td></tr>
<tr><td>10 year</td><td>38</td><td>40</td><td>47</td><td>46</td></tr>
<tr><td>P value</td><td colspan="2">0.04</td><td colspan="2">0.47</td></tr>
<tr><td colspan="5">Patient survival (%)</td></tr>
<tr><td>1 year</td><td>92</td><td>95</td><td>93</td><td>95</td></tr>
<tr><td>3 year</td><td>84</td><td>89</td><td>86</td><td>88</td></tr>
<tr><td>10 year</td><td>60</td><td>57</td><td>57</td><td>63</td></tr>
<tr><td>P value</td><td colspan="2">0.58</td><td colspan="2">0.06</td></tr>
</table>
*Rejection was biopsy proven
</td></tr>
<tr><td>Pine[7]
2010</td><td>DCD (n = 103) vs DBD (n = 183)
(unadjusted analysis: patients matched on recipient and donor age, sex, and BMI; HLA mismatches; ischemia time; immunosuppressive regimen)

Delayed graft function
58% vs 28%, P = 0.03

Primary non-function
4% vs 1%, P = 0.04

Biopsy proven acute rejection
12% vs 16%, P = NS

1 year/3 year graft survival
97% vs 96% / 85% vs 86%, P = 0.30

1 year / 3 year recipient survival
98% vs 97% / 92% vs 95%, P = 0.12</td></tr>
<tr><td>Singh[12]
2011</td><td>DCD (n = 70) vs DBD (n = 508) (unadjusted analysis)

Delayed graft function
40 (57%) vs 109 (21%); P = 0.0001

Biopsy-proven acute rejection
20 (29%) vs 82 (16%); P = 0.018

Overall graft survival
54 (77%) vs 402 (79%); NS

Death-censored graft loss
10 (15%) vs 68 (13%); NS</td></tr>
</table>

First Author, Publication Year	Main Study Findings
	Overall patient survival 62 (89%) vs 456 (90%); NS
Snoeijs[3] 2010	**DCD vs DBD** Adjusted analysis (patients matched on transplant type, year and other key characteristics) Delayed graft function (N = 726) OR 10.3; 95% CI, 6.68 to 15.9; *P* <0.001 Primary non function (N = 811) OR 7.51; 95% CI, 4.01 to 14.1; *P* <0.001 Death-censored graft loss at 15 years (N = 851) HR 1.82; 95% CI, 1.37 to 2.42; *P* <0.001 Patient survival at 15 years (N = 857) HR 1.16; 95% CI, 0.87 to 1.54; *P* = 0.32 eGFR at 1 year (N = 646) mean difference -6.2 mL/min; 95% CI, -9.4 to -3.0); *P* <0.001
Snoejis[13] 2010	**DCD (n = 459) vs DBD (n = 680)** Graft failure in first 3 months (unadjusted) 12.0% vs 6.3%; *P* = 0.001 Mortality rate, % per patient-year (unadjusted) DCD 3.4% vs DBD 3.7% vs dialysis 5.0%, *P* value not reported Mortality rate (adjusted analysis) Standard criteria DBD vs dialysis treatment HR 0.51; 95% CI, 0.32 to 0.81; *P* = 0.004 Standard criteria DCD vs conventional therapy† HR 0.44; 95% CI, 0.24 to 0.80; *P* = 0.007 Extended criteria* DBD vs conventional therapy† HR 1.12; 95% CI, 0.71 to 1.76; *P* = 0.62 Extended criteria* DCD vs conventional therapy† HR 0.61; 95% CI, 0.31 to 1.19; *P* = 0.15 †conventional therapy defined as dialysis treatment or waiting on dialysis until standard criteria DBD transplantation (follow up continued after receipt of DBD kidney) *extended criteria donors were ≥60 years or between 50 and 60 years

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings</th></tr>
<tr><td></td><td>with two additional risk factors (elevated creatinine, hypertension or cardiovascular cause of death)</td></tr>
<tr><td>Summers[8]
2010</td><td>DCD vs DBD for all transplant recipients
(unadjusted)

Delayed graft function
332/659 (50%) vs 1386/5474 (25%); P <0.0001

Acute rejection in first 3 months
121/723 (17%) vs 1646/6793 (24%); P <0.0001

DCD (n = 739) vs DBD (n = 6759) for first transplant recipients
Graft failure up to 5 years (adjusted)
HR 1.01; 95% CI, 0.83 to 1.19; P = 0.97</td></tr>
<tr><td>Barlow[9]
2009</td><td>NHBD (n = 112) vs HBD (n = 164)
(unadjusted analysis; patients matched for cold ischemia time, HLA mismatches, donor age, prior transplant and 2 of 4 minor criteria)

Delayed graft function
94 (83.9%) vs 36 (22.0%); P <0.001

Primary non-function
6 (5.4%) vs 3 (1.8%); P = 0.164

Biopsy proven acute rejection
33 (29.5%) vs 63 (38.4%); P = 0.157

<table>
<tr><td></td><td colspan="2">Death-censored graft survival (%)*</td><td colspan="2">Graft and patient survival (%)†</td></tr>
<tr><td>Year</td><td>DCD</td><td>DBD</td><td>DCD</td><td>DBD</td></tr>
<tr><td>1</td><td>92</td><td>91</td><td>86</td><td>88</td></tr>
<tr><td>3</td><td>82</td><td>89</td><td>76</td><td>82</td></tr>
<tr><td>5</td><td>78</td><td>86</td><td>69</td><td>76</td></tr>
<tr><td>10</td><td>61</td><td>72</td><td>50</td><td>58</td></tr>
<tr><td>15</td><td>44</td><td>59</td><td>29</td><td>44</td></tr>
<tr><td>P value</td><td colspan="2">0.052</td><td colspan="2">0.22</td></tr>
</table>
*graft failures are events; †graft failure or death are events in these time to event analyses

serum creatinine was significantly higher in NHBD recipients at 1 (P = 0.009), 2 (P = 0.009), 11 (P = 0.038), and 12 (P = 0.010) years and not significantly different at all other time points (0.25 to 15 years).</td></tr>
</table>

DBD = donation after brain death; DCD = donation after cardiocirculatory death; DCGL = death-censored graft loss; DCGS = death-censored graft survival; DGF = delayed graft function; eGFR = estimated glomular filtration rate; HBD = heart beating donor; HR = hazard ratio; NHBD = non-heart beating donor; NS = not significant; OR = odds ratio

APPENDIX 5: Clinical Practice Guidelines

Reason for exclusion - did not meet criteria for evidence-based guidelines

1. Chinese Society of Organ Transplantation, Chinese Medical Association. National guidelines for donation after cardiac death in China. Hepatobiliary Pancreat Dis Int. 2013 Jun;12(3):234-8.
PubMed: PM23742766

2. O'Rourke J. Non heart beating organ donation in adults: a clinical practice guideline. Ir Med J. 2013 Jun;106(6):186-8.
PubMed: PM23909159

3. Reich DJ, Mulligan DC, Abt PL, Pruett TL, Abecassis MM, D'Alessandro A, et al. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. Am J Transplant. 2009 Sep;9(9):2004-11.
PubMed: PM19624569