Donation after circulatory death: current status

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Purpose of review
Donor shortage has forced transplant teams to explore new methods to increase the potential donor pool. Donation after circulatory death (DCD) has opened new perspectives and could be a valuable option to expand the brain-dead donors. The purpose of this review is to provide an overview of current practice and to identify remaining questions related to ethical and medical issues that should be further addressed in the future.

Recent findings
Recent findings demonstrate acceptable outcomes after DCD kidney and lung transplantation but inferior graft survival for liver transplantation. The impact and importance of the agonal phase following withdrawal of treatment in controlled DCD is increasingly recognized. Premortem interventions are currently under debate related to preservation strategies or comfort therapy. New preservation strategies using in-situ/in-vivo extracorporeal membrane oxygenation or ex-vivo machine perfusion have large potential in the future. Finally, organizations and institutions are reporting more uniform guidelines related to declaration of death and DCD organ procurement.

Summary
DCD donation has regained much attention during the last decade and is now part of standard clinical practice albeit this type of donation should not be regarded as an equally acceptable alternative for donation after brain death. It will be important to further explore the potential of DCD, to monitor the long-term outcomes and to further optimize the quality of these grafts. Development and implementation of uniform guidelines will be necessary to guarantee the clinical use of these donor pools.

Keywords
agonal phase, donation after circulatory death, nonheart-beating donor, organ preservation, transplantation

INTRODUCTION

To expand the donor pool, the number of organ transplantations from donation after circulatory death (DCD) donors, also frequently referred to as nonheart-beating donors (NHBD) or death after cardiac death donors, rapidly increased over the last decade. DCD donation takes place after declaration of death based on cardiorespiratory criteria in contrast to donation after brain death (DBD) in which neurological criteria are used. Organs from these DCD donors inevitably sustain warm ischemic damage. Consequently, DCD kidneys are more susceptible to delayed graft function without impaired long-term outcome while DCD liver grafts experience inferior graft survival mainly related to higher rates of biliary strictures. In contrast, DCD lungs seem to do equally as well as grafts from DBD donors. On the contrary, DCD organ donation should not be seen as an equally acceptable alternative to brain-dead donors because it yields less organs (e.g. pancreas and heart).

In addition, using DCD donors has challenged the medical, ethical and transplant community on several grounds. Pitfalls include the definition of cardiac or circulatory death and its irreversibility. Also, the exact impact of the agonal phase and the ongoing hemodynamic instability contributing to the so-called warm ischemic damage is still not well defined.

Furthermore, during the end of life care and the withdrawal phase, adequate comfort should be guaranteed to the dying patient whilst at the same time, organ protective measures could be taken during this period. Finally, simple cold storage, the

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KEY POINTS

- Donation after circulatory death is an accepted strategy to expand the potential donor pool.
- DCD donors have challenged the medical, ethical and transplant community with the definition of cardiac or circulatory death, the exact impact and management of the agonal phase and the ongoing hemodynamic instability contributing to the so-called warm ischemic damage.
- New organ preservation methods to better protect and recondition DCD organs are being developed including in-situ normothermic recirculation before, or ex-situ machine perfusion preservation after organ procurement.

current gold standard of organ preservation, has proven to be insufficient to optimally preserve organs from DCD donors. New organ preservation methods to better protect and recondition DCD organs are thus being developed including in-vivo normothermic recirculation using extracorporeal membrane oxygenation (ECMO), or ex-vivo machine perfusion preservation after organ procurement, respectively.

This review aims to give an overview of the pitfalls that are encountered during DCD organ donation whilst reporting on recent new insights and developments.

CLASSIFICATION OF DONATION AFTER CIRCULATORY DEATH DONORS

At the First International Workshop on NHBD organized by G. Kootstra in Maastricht [1] four types of DCD donors were identified. (Table 1). Categories I (dead on arrival) and II (unsuccesful resuscitation) comprise the 'uncontrolled donors'. Categories III (awaiting cardiac arrest) and IV (cardiac arrest in brain-dead donor) comprise the 'controlled donors'. In contrast to DBD donors in which the organs are perfused until the moment of preservation, organs from DCD donors suffer from warm ischemia between circulatory arrest and the start of organ cooling. This warm ischemic interval might lead to organ damage, increase the severity of ischemia-reperfusion injury and result in post-transplant graft dysfunction or failure.

Table 1. Classification of nonheart-beating donors

Category I	Dead on arrival	Uncontrolled
Category II	Unsuccessful resuscitation	
Category III	Awaiting cardiac arrest	Controlled
Category IV	Cardiac arrest in brain-dead donor	

Classification of nonheart-beating donors according to the Maastricht classification, initially developed by Kootstra *et al.* Table 1 is adapted from [1] and original work.

Uncontrolled DCD (uDCD) occurs when a person dies unexpectedly. The exact length of the warm ischemic period is often not known.

In the controlled DCD (cDCD) donor, the moment of withdrawal of life-sustaining therapy leading to circulatory arrest can be planned in advance, and therefore the length of the warm ischemic interval is known more precisely. Nowadays, the majority of DCD donors are category III DCD donors. Potential cDCD donors are patients suffering severe, irreversible brain damage but do not fullfill the criteria of brain death. The decision is made that life-sustaining therapy (disconnection of cardiovascular support and mechanical ventilation) will be withdrawn prior to and completely independent from the option of organ donation. Imminent death is anticipated and these patients become a donor after cessation of circulation respecting the 'Dead Donor Rule'. Ideally, this takes place in the operating room.

Another more updated classification including modified categories was recently proposed [2▪] to better define the exact circumstances of the circulatory arrest and consequent warm ischemic organ damage.

WARM ISCHEMIC INTERVAL

Currently, there is no clear, nor uniform definition of the warm ischemic interval. Variable definitions have been suggested and they vary from the time when the warm ischemia is thought to start. The start of the warm ischemia may include the moment of withdrawal, a systolic or mean arterial pressure below a certain value (referred to as onset of hemodynamic instability or organ hypoperfusion), or cardio-circulatory arrest and ends with the start of cold perfusion [3▪,4–6]. Moreover, the method utilized to determine cardio-circulatory arrest may or may not substantially prolong the warm ischemia (cfr determination of death).

An accurate definition of warm ischemia in DCD is important because the associated injury is known to be deleterious to subsequent graft function besides the relevance of using uniform definitions. Currently, there is a tendency to define and register the warm ischemia at the onset of hemodynamic instability (referred to as 'functional warm ischemia') since organ perfusion may be compromised from that time point on [7▪▪]. The situation becomes even more complicated when prolonged cardiopulmonary resuscitation (CPR) or

ECMO are installed in uncontrolled DCD [8▪]. Recommendations are awaited within the transplant community in the near future. Potential conflicts using different definitions are illustrated in (Fig. 1).

AGONAL PHASE AND COMFORT THERAPY

After withdrawal of life-sustaining therapy in cDCD, a variable period of progressive hypoxia and hypotension develops until the onset of circulatory arrest and determination of death defined as the agonal phase. So far, most experimental DCD studies used a model of sudden cardiac arrest. However, in clinical practice, concerns have been raised about the injury that may occur to the donor graft in the agonal period or withdrawal phase before circulatory arrest. The importance of this agonal phase is dual. First, concerns have been raised about potential physical and psychological suffering imposed on the donor and how to provide optimal comfort therapy. Second, prolonged cardiopulmonary instability during this phase may result in unsuccessful organ procurement because of additional graft injury jeopardizing outcome of the recipient.

One critical aspect of the agonal phase is administration of comfort therapy. As this applies to palliative care, the principle of double effect supports the administration of treatments with the intent to support patient comfort and alleviate suffering, even if there is a risk of hastening death. Overall, data indicate that time to death after withdrawal of life-sustaining therapy to allow organ donation is mostly limited to 60 min. Occasionally, longer intervals up to 3 days have been reported [9]. Therefore, relatives should be informed about this possibility and protocols should consider these cases.

Currently, there are no useful guidelines to assist the method of withdrawal of therapy and only general principles are provided. An interesting case series demonstrated significant changes in the bispectral index values immediately after withdrawal of care which where consistent with lighter planes of anesthesia [10]. This finding might warrant the use of hypnotic or anesthetic drugs in these patients. Interestingly, the fear to hasten death is not supported by the analysis of DeVita *et al.* [11] showing that their use was associated with decreased risk of dying within 60 min after withdrawal. Although poorly documented, no relation could be demonstrated between quantities of sedatives and analgetics and time to death [11,12▪,13,14]. Another interesting strategy could be the swith of analgetics and sedatives to volatile anesthetics in the operting room thereby providing additional pharmacological preconditioning to the organs retrieved [15]. Overall, there is no consensus and the issue of comfort therapy deserves more attention in the future, preferably an international guideline.

Besides comfort therapy, the need to administer heparin premortem to the DCD donors remains controversial and some countries do not legally accept any form of premortem intervention. Also, the need for heparin administration and the timing (premortem or postmortem with additional chest compressions during uDCD) remains unsure and the incidence of postmortem thrombi seems to be very low. So far, no data support a potential hastening of death due to heparin [16▪,17▪,18,19,20▪,21–23,24▪].

Historically, most studies have not investigated the impact of the withdrawal phase (hypoxic arrest, sudden cardiac arrest, exsanguination, duration) on graft function. Most transplant programs will limit the agonal phase or withdrawal phase to 60–90 min to exclude potential harmful effects. Data however are still very limited.

Profound hemodynamic instability rather than the total duration of the withdrawal phase might be more important and has a negative impact on kidney graft function and liver outcome [25].

Other articles on longer intervals from the time of withdrawal to asystole revealed an immediate effect on kidney graft survival, without detrimental effect on long-term outcomes [26]. However, no effect could be detected in the study of Reid *et al.* [27].

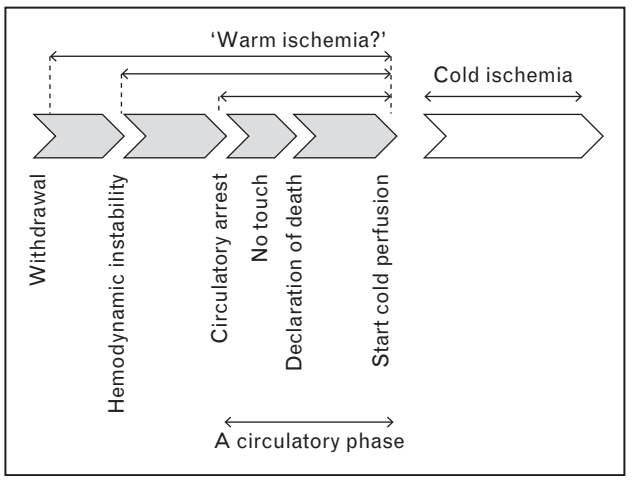

FIGURE 1. Definition of warm ischemic interval. Different definitions of warm ischemic interval. The warm ischemic interval may vary according to the choice of onset. Different opinions have been suggested. Currently, the interval between 'hemodynamic instability' and 'start of cold perfusion' is referred to as 'functional warm ischemia'. Figure 1 is original work.

The impact of a longer period of instability might become more important in case of liver transplantation. In a porcine model of DCD with hypoxic arrest, histological changes were significant [28]. Clinically, the agonal phase does not seem to influence the development of ischemic cholangiopathy [29▪▪].

An interesting experimental large animal study [30] addressed specifically the mode of death in the DCD donor. In this porcine model, pulmonary grafts were of inferior quality following hypoxic cardiac arrest compared with circulatory arrest after exsanguination. Also, hypoxic arrest resulted in a significant catecholamine storm comparable to brain-dead donors [31].

In their clinical series, however, Levvey *et al.* [4] did not observe a hypertensive phase after withdrawal of treatment and they postulated that the absence of this sympathetic response was probably due to the severity of underlying brain injury and the use of sedatives and narcotics.

PREDICTION OF DEATH AND IDENTIFICATION OF POTENTIAL DONORS

Predicting the time to donor asystole would enable resources to be directed to procurements more likely to be successful and would optimize the quality of DCD grafts. The University of Wisconsin [32] has developed an algorithm to assess the potential cDCD donor. This score is computed based on patient's age, BMI, O_2 saturation, method of intubation (endotracheal vs. tracheostomy), level of spontaneous respiration and requirement for vasopressors, all of which indicate the likelihood of death within 1 h after extubation. Potential criticism to this widely used scoring system is the absence of prospective validation studies and the fact that this algorithm is constructed based on a weaning protocol. United Network for Organ Sharing (UNOS) has also developed criteria that can be helpful in identifying potential DCD candidates (Table 2) [33] and these criteria have been validated by DeVita *et al.* [11]. They concluded that patients with no criteria might be excluded from consideration for DCD. Those with more than one criterium are reasonable candidates, while those with a single criterium should be considered if a 50% failure rate for DCD is acceptable. In addition, they defined two simple and accurate rules with high specificity and sensitivity for death within 60 min: either a Glasgow Coma Scale (GCS) of 3 or the combination of a SaO_2/FiO_2 ratio less than 230 and a peak inspiratory pressure of more than 35 cmH_2O. For cDCD kidney donors, Suntharalingam *et al.* [9] observed that higher age, the mode of ventilation (not pressure support) and higher FiO_2 were associated with a shorter time to death. Pine *et al.* [34] showed that donors with a high MAP (102 mmHg for unsuccessful vs. 92 mmHg for successful) at treatment withdrawal were more likely to fail to progress to circulatory arrest. Davilla *et al.* developed a prediction model for cardiac arrest and graft usability in controlled liver DCD donors; age more than 40 years, use of inotropes, high sodium levels and the presence of gag or cough reflexes were found to be important protective factors for cardiac arrest [35▪▪]. In contrast, in a prospective study of cDCD donors, Wind *et al.* [12▪] could not clearly identify any risk factors for death within 60 min except from mechanical ventilation.

Most prediction models are tailored with respect to pulmonary and circulatory support. Uncounted variables are often the addition of comfort therapy and the presence or absence of upper airway reflexes. As potential (controlled) DCD donors also suffer

Table 2. United Network for Organ Sharing criteria for identifying potential donation after circulatory death patients

Apnea	LVAD	PEEP $\geq$ 10 and $SaO_2 \leq 92\%$	Norepinephrine, epinephrine or phenylephrine $\geq$ 0.2 μg/kg/min	IABP 1 : 1 OR (dobutamine or dopamine $\geq$ 10 μg/kg per min and CI $\leq$ 2.2)
RR < 8	RVAD	$FiO_2 \geq 0.5$ and $SaO_2 \leq 92\%$	Dopamine $\geq$ 15 μg/kg/min	IABP 1 : 1 and CI $\leq$ 1.5
RR > 30 during trial of mechanical ventilation	V-A ECMO	V-V ECMO		
	Pacemaker with unassisted rhythm < 30			

This classification has been introduced during a National Conference on Donation after Cardiac Death and has subsequently be validated [11,33]. Patients with more than one criterium are reasonable candidates, while those with a single criterium should be considered if a 50% failure rate for DCD is acceptable. RR, respiratory rate; LVAD, left ventricular assist device; RVAD, right ventricular assist device; V-A ECMO, venoarterial extracorporeal membrane oxygenation; PEEP, positive end-expiratory pressure; SaO_2, arterial oxygen saturation; FiO_2, fraction of inspired oxygen; V-V ECMO, venovenous extracorporeal membrane oxygenation; IABP, intra-aortic ballon pump; CI, cardiac index. Table 2 is adapted from [11] and original work.

from some degree of brain damage, Rabinstein *et al.* [36▪▪,37▪] developed a DCD-N score ('donation after cardiac death in patients in a neurocritical state' score) based on mainly neurological criteria. They assigned two points for absent cough reflex and one point each for absent corneal reflexes, absent or extensor motor response to pain, and oxygenation index of more than 3.0. A score of 3 or more translated into a 74% probability of death within 60 min.

Another question regarding the withdrawal of life support is whether extubation of the patients will hasten death. Evidence is circumstantial and there are no controlled studies [7▪▪,38▪].

An important factor that should be considered more in the future is the potential window of opportunity to withdraw life support. The timing of withdrawal during a specific phase of stability or instability may largely influence the dying process [38▪].

DETERMINATION OF DEATH

DCD donors are declared dead using circulatory–respiratory criteria. In a nontransplant setting, this is a straightforward criterium in the absence of resuscitation attempts. Potential controversies emerge when a potential DCD organ donor is identified and the decision for withdrawal of life-sustaining therapies is made. Identification of the precise moment of death is necessary in order to comply with the 'Dead Donor Rule' (i.e donors of vital organs must be declared dead before organ removal rather than dying as a result of donation) [39]. In addition, the transplant team wants to procure organs as soon as possible in order to limit the warm ischemic interval. A large debate is ongoing among researchers and the general public about the criteria for the determination of death [40▪,41▪].

The first issue is how to determine death. A survey investigating regional differences learns that there is no consensus among professionals how to define circulatory death. Most institutions refer to the irreversible cessation of circulation and respiration and there is a scarcity of well conducted studies [42]. The determination of circulatory arrest is based on indirect measures of circulatory arrest (absent heart sounds, absent pulse, absent blood pressure, absent breathing, absent neurological function) but the majority of guidelines require specific diagnostic procedures [43▪,44▪▪]. Most often, invasive arterial monitoring is required or advised in a DCD setting. With respect to ECG monitoring, pulseless electrical activity may occur and should be compatible with circulatory death and organ procurement.

Another concern related to the exact timing of declaration of death and the fear to violate the 'Dead Donor Rule' is the occurence of autoresuscitation (defined as the spontaneous return of antegrade circulation). Hornby *et al.* [45] reviewed the articles on autoresuscitation and found that the limited cases were in a setting of failed CPR (which would be the case in uDCD). In case of withdrawal of life-sustaining therapy without CPR (comparable to cDCD), no cases have been reported. A recent study [46▪▪] in DCD donors showed that no autoresuscitation occured within a period of 2 min.

In all DCD protocols, a strict interval is respected between the circulatory arrest and the declaration of death. This critical interval, the so-called 'no touch' period varies between 2 and 10 min, and most centers use 5 min.

However, there is still a lot of controversy and discussion whether these patients can be really declared dead after this interval.

Our concept of death is dichotomized and many accept the definition as stated in the Uniform Determination of Death Act (UDDA) [47]: 'An individual who has sustained either irreversible cessation of circulatory and respiratory functions or irreversible cessation of all function of the entire brain, including the brain stem, is dead'. Healthcare professionals struggle with the concept of 'irreversible', because resuscitation attempts might still be efficient and restore circulation to the brain. In a very clear discussion, Bernat [48] introduced the distinction between 'irreversible' and 'permanent' to answer this issue. 'Permanent' means that the cessation of the circulation will not be restored, neither spontaneously, nor as the result of resuscitation efforts that are not attempted. All functions that are 'permanently' lost will rapidly become 'irreversible'. So, in the setting of DCD donation, a patient can be declared dead based on a 'permanent' situation. It also explains the meaning of the 'no touch' interval as a period to observe 'no autoresuscitation' rather than a period to develop 'irreversible' brain death.

THE FUTURE OF DONATION AFTER CIRCULATORY DEATH ORGAN DONATION

DCD organ donation found its way into clinical practice, however some important aspects will need further attention in the future such as the preservation of the organs inside the donor, preservation and evaluation outside the donor using machine perfusion and the application of DCD protocols to a specific group of patients with request for euthanasia [49▪▪].

IMPROVED ORGAN PRESERVATION TECHNIQUES

In cDCD, the worldwide most often used technique for organ preservation of abdominal organs is the 'modified super-rapid technique' as described by the Pittsburgh group [50]. This consists of a midline laparotomy followed by a rapid cannulation of the aorta to start the cold flush.

An alternative is the premortem cannulation of the femoral artery using a double balloon triple lumen catheter and insertion of a catheter in the femoral vein for venous decompression [51].

Organ preservation from uDCD donors might be different and a large experience has been built in Spain and France. When a case of circulatory arrest is notified, advanced life support is initiated and, if the circulatory arrest is considered irreversible, CPR can be continued until arrival in the hospital (most often using mechanical chest compression devices). After declaration of death (including an interruption of resuscitation maneuvers) and a maximum period of chest compressions of 120 min, the donor can be connected to a cardiopulmonary bypass system by femoral cannulation (normothermic ECMO, extracorporeal membrane oxygenation) to preserve the abdominal organs (for a maximum of 240 min.). This allows further organization to proceed with organ procurement by hypothermic perfusion [52▪,53–55]. Other protocols for uDCD have also adopted the technique of cold ECMO [56] or the insertion of a double balloon catheter followed by in-situ cold flush of the organs and explantation [57]. Recently, a protocol for New York city has also been developed using normothermic ECMO [58▪]. Importantly, when ECMO is introduced for organ preservation, recirculation of blood to the brain should be avoided by means of a balloon inserted via the contralateral femoral artery and inflated at the level of the diaphragm ensuring that the patient's condition is irreversible [59▪]. Whether ECMO is superior to protect the organs and influences the ischemic damage is stil not well studied.

With respect to preservation of pulmonary grafts, cooling of the lungs inside the cadaver is an attractive way to preserve the organ in the interval between cardiac arrest and ex-situ cold storage [60]. This technique is currently referred to as topical cooling and is achieved by continuous infusion of cold preservation solution via intrapleural drains (uDCD) [61▪] or via rapid sternotomy (cDCD) [62▪]. Some centers will proceed directly with cannulation and cold perfusion after a rapid sternotomy in cDCD when the warm ischemic interval is expected to be short [63▪,64▪].

MACHINE PERFUSION

A common question in the setting of DCD donation is the quality of the organs retrieved. In contrast to brain-dead donors, it is often not possible to evaluate the organs inside the donor because of the absence of circulation or the strict time intervals applied. In recent years, machine perfusion has gained increased interest in order to evaluate and recondition solid organs before transplantation and DCD procurement has given a new impulse to the use and development of clinical devices [65▪▪–67▪▪].

The principle of machine perfusion is based on the recirculation of a specific solution in a circuit outside the body. Machine perfusion offers the potential for better organ preservation and resuscitation but may also allow real-time monitoring of the graft function using physiological and molecular markers. A recent clinical trial [68▪▪] clearly demonstrated a benefit (reduced delayed graft function and higher creatinine clearance) for hypothermic machine perfusion in controlled DCD kidneys over static cold storage. These data were not confirmed in a smaller study [69]. A recent review concluded that pulsatile machine perfusion of DCD kidneys reduced delayed graft function rates with no benefit in one year graft survival [70]. There are currently no data on the benefit of machine perfusion of livers in DCD organs and only one clinical feasibility study has been performed in brain-dead donors with a reduction of inflammation, ultrastructural damage and early allograft dysfunction in the hypothermic machine perfusion group compared with a historical static cold perfusion group [71]. In lung transplantation, machine perfusion (also refered to as EVLP, ex-vivo lung perfusion) was initially developed by Steen *et al.* [72,73] to evaluate lungs from DCD donors. The technique of EVLP has been extensively studied and is mainly used to investigate lungs that were previously considered unacceptable [74▪▪,75▪]. Evidence comparing classical cold storage with EVLP in DCD settings is still limited [76].

FURTHER EXPANSION OF THE DONATION AFTER CIRCULATORY DEATH DONOR POOL

A very specific group of DCD donors are donors that die following physician assisted death or euthanasia. Although euthanasia is prohibited in most countries, there is a legal and ethical framework in Belgium and the Netherlands that allows the intentional termination of life when a patient is in a medically futile condition and in constant unbearable physical or mental suffering. In Belgium,

four cases of organ donation after euthanasia have been reported following patients' voluntary and repeated expression of their strong will to donate their organs [77]. These procurements were carried out using a DCD protocol and could have a substantial potential in countries that allow euthanasia. This practice also opened a wider controversial ethical discussion if in some cases (permanent vegetative state or anencephalic infants), we should wait until the patients have died as a result of withdrawal of life support. Alternatively, these patients could be anaesthetized followed by removal of their organs with the argument that they cannot be harmed as their biographical life has ended. This practice could also be less associated with suffering for the patient than death following withdrawal of life support. Of course, this is a theoretical discussion and conflicts with the 'Dead Donor Rule' and the 'nonkilling' principle. However, this would lead to one individual (the receptor) being 'better off' and no individual would be 'worse off' (the donor), as these donors are on life support and the decision has been made to stop therapy [78▪▪].

CONCLUSION

DCD organ donation is a valuable approach to extend the donor pool and increasing DCD practice is reported worldwide. The absence of uniform guidelines has often left professionals in doubt about ethical, legal and medical aspects. However, the transplantation community has recognized these pitfalls and more guidelines and uniform procedures are now reported. Important questions regarding withdrawal of life-support and end of life are currently under debate. New practices with respect to organ preservation are constantly developed and initial clinical trials are conducted. We believe that historical fundamental issues and questions are gradually solved and that professional healthcare providers will become more confident with this valuable pool of organs in order to save the lives of many potential recipients.

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Conflicts of interest

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D.V.R. is a consultant for Transmedics, Andover, MA currently acting as prinicipal investigator of the Expand Registry. He received research support from XVIVO Perfusion AB (previously Vitrolife), Göteborg, Sweden in the past.

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- ▪▪ of outstanding interest

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