Clinical Trial Protocol

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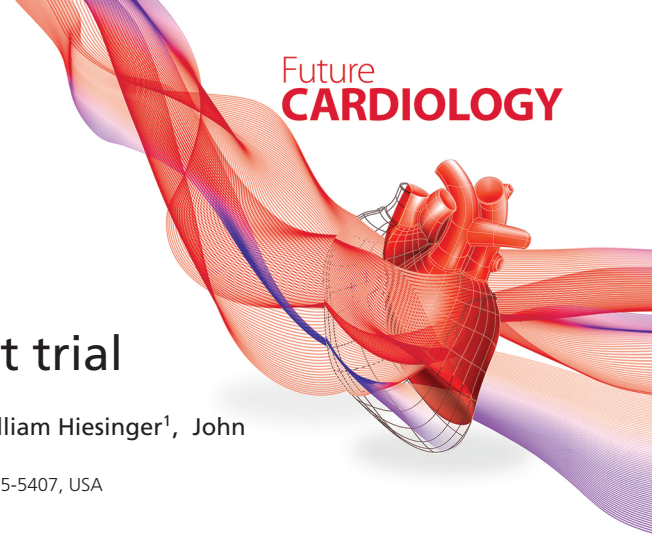

Donors after circulatory death heart trial

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Orthotopic heart transplantation is the gold standard treatment for end-stage heart failure. However, the persistent shortage of available donor organs has resulted in an ever-increasing waitlist and longer waiting periods for transplantation. On the contrary, increasing the number of heart transplants by preserving extended criteria donors and donation after circulatory death hearts with the Organ Care System™ (OCS) Heart System has the potential to provide the gold standard, life-saving treatment to patients with end-stage heart failure. The objective of the Donation After Circulatory Death Heart Trial is to evaluate the effectiveness of the OCS Heart System to preserve and assess hearts donated after circulatory death for transplantation to increase the pool of donor hearts available for transplantation, which can potentially provide patients with end-stage heart failure with the life-saving treatment.

Clinical Trial Registration: NCT03831048 (ClinicalTrials.gov)

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We are currently facing a pandemic of patients with end-stage heart failure [1]. Many treatments have been developed for patients with end-stage heart failure, among which orthotopic heart transplantation remains the criterion standard [2]. However, the persistent shortage of available donor organs has resulted in an ever-increasing waitlist for transplantation, as well as longer waiting periods before surgery. Although >20,000 patients in the USA may benefit from heart transplantation per year, only 3000 will receive a new heart, with a waitlist mortality of 10.7 deaths per 100,000 waitlist-years [3].

Because of such persistent and worsening shortage of available donor hearts, for the past several decades, there has been scientific and clinical interest in the development of *ex situ* heart perfusion with oxygenated and nutrient enriched blood to reduce ischemic injury to the donor heart and potentially enable *ex situ* assessment of metabolic and mechanical function [4]. More recently, *ex situ* heart perfusion has been used to potentially expand the donor pool to include hearts from donation after circulatory death (DCD) [5].

Until recently, beating hearts from donation after brain death (DBD) donors were the only heart donors used for transplantation worldwide. However, during the last 20 years, the number of suitable DBD donors has plateaued while the number of patients diagnosed with end-stage organ failure continues to increase. As a result, the waiting list for organ transplantation has grown. To address the organ shortage, DCD donors are being increasingly used to procure donor lungs, livers and kidneys.

However, due to potential damage of warm ischemia in the donor and the functional arrest of the heart that may never recover, DCD donors are not utilized for adult heart transplantation in the USA. In contrast, international transplant centers have been successfully transplanting hearts from DCD donors, using the Organ Care System™ (OCS) Heart System for preservation and assessment of these hearts prior to transplantation (Figure 1).

Introduction to the trial

With regard to the challenges posed by DCD donor hearts noted, the OCS Heart System offers the following advantages and capabilities:

- Preservation of the DCD heart into beating physiologic state *ex situ* to enable for the assessment of the donor heart's viability;

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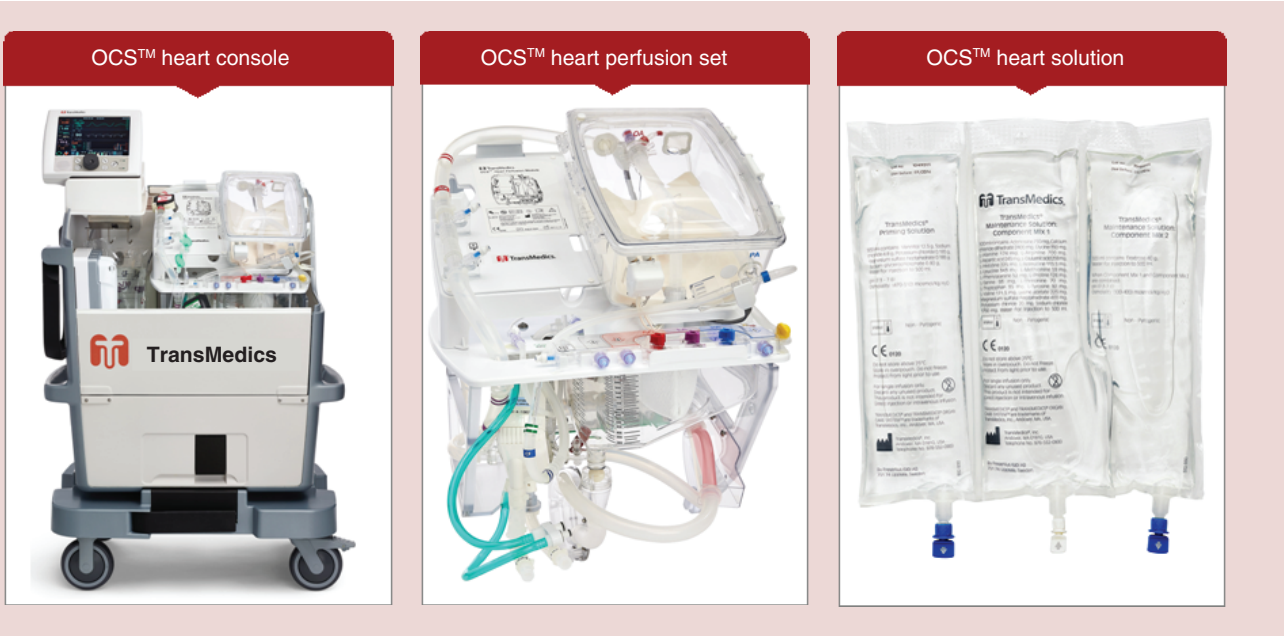

Figure 1. Organ Care System™ Heart System, including console, perfusion set and solution.
OCS: Organ Care System.
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- Reduction of the time-dependent ischemic injury to the donor hearts during preservation, thus eliminating significant logistical and geographical barriers to heart transplantation that currently exist with cold storage preservation;
- Optimization of donor heart *ex situ* environment by optimizing oxygen and substrate delivery, while also replenishing key hormones and nutrients that are depleted due to the brain-dead condition in the body of the donor, which would negatively impact cardiac function if not replenished;
- Assessing the adequacy of the perfusion and metabolic condition of the donor heart utilizing standard lactate levels to allow physicians to judge the suitability of the organ for transplantation using the standard criteria that physicians currently use when harvesting the organ from the donor, thus substantially minimizing the risk of transplanting poor hearts into recipients.

In summary, patients listed for heart transplantation due to their end-stage heart disease are suffering from a terminal, life-threatening condition. Increasing the number of heart transplants by preserving extended criteria donors and DCD hearts with the OCS Heart System has the potential to provide listed patients with the life-saving treatment.

Background & rational

Currently, only DBD donors are utilized for adult heart transplantation in the USA, because of ethical and legal issues related to DCD. In contrast, international transplant centers have been procuring hearts from DCD donors, using the OCS Heart System for preservation, and assessment prior to transplantation. The OCS Heart System can minimize the detrimental effects of ischemia, because it perfuses the donor heart with warm oxygenated blood. It enables the heart to be resuscitated to a full beating state, and importantly, it enables the transplant team to assess metabolic (lactate production) and perfusion parameters of these hearts to determine their suitability for transplantation. These capabilities are critical when using marginal/questionable and DCD donor hearts to minimize the risks on the recipients receiving these organs.

Messer *et al.* have published the results of a study of the OCS Heart System for preserving DCD donor hearts in the UK [5]. This was a single-center observational matched cohort study comparing consecutive patients who received transplants of DCD donor hearts between 1 February 2015 and 31 March 2017, versus matched recipients who received transplants of DBD donor hearts between 1 February 2013 and 31 March 2017. There

was no difference in implant technique or immunosuppressive regimens during this period. DCD hearts were transported and continually perfused on the OCS Heart System. DBD hearts all underwent the current standard of direct procurement and cold storage until transplantation.

DCD heart donors were restricted to Maastricht Category III donors, defined as expected death after the withdrawal of life-supportive therapy. A retrospective cohort of DBD heart transplants, matched for donor and recipient characteristics, was used as a comparison group. The primary outcome measure of this study was 90-day survival. There were 26 DCD heart transplants performed during the 25-month study period. The use of the OCS Heart System resulted in an 86.7% rate of successful utilization of DCD hearts for transplantation. Survival at 90 days was not significantly different between DCD and matched DBD transplant recipients (DCD, 92%; DBD, 96%; p = 1.0). Hospital length of stay, treated rejection episodes, allograft function and 1-year survival (DCD, 86%; DBD, 88%; p = 0.98) were comparable between groups.

Of the 26 DCD hearts transplanted, 12 used normothermic regional perfusion (NRP) before OCS and 14 used direct procurement and preservation (DPP). During the NRP procedure, following circulatory arrest, the cerebral circulation was terminated but perfusion was restored to the thoracic and abdominal organs within the donor body. Functional assessments of the heart were performed after which donor blood was collected and the heart was arrested with cold cardioplegia. (NRP will not be used in this study). The DPP procedure followed the standard OCS blood collection and cardioplegic arrest of the donor heart. In the DPP arm, utilization was 77.8% (14/18) and 90-day survival was 86% (12/14).

The authors noted that DCD heart transplantation may increase heart transplants by 17–30%. During the study period, 84 DBD heart transplants were performed at this institution and the 26 additional DCD heart transplants increased the number of transplants by 33%. The authors concluded that the adoption of DCD heart transplantation can be safely implemented into widespread routine clinical practice.

Dhital *et al.* have reported the transplantation of DCD hearts into three recipients (two men, one woman; mean age 52 years) [7]. They received Maastricht Category III controlled hearts donated after circulatory death from people younger than 40 years and with a maximum warm ischemic time (WIT) of 30 min. Donor heart WITs were 28, 25 and 22 min, with OCS Heart perfusion times of 257, 260 and 245 min, respectively. Two patients needed temporary mechanical support postoperatively. All three recipients had normal cardiac function within a week of transplantation, and, at the time of the report, were alive and recovering well at 176, 91 and 77 days after transplantation.

Subsequently, it has been reported that the experience of using the OCS Heart System to preserve DCD hearts at St. Vincent's Hospital in Sydney, Australia. The donors were Maastricht Category III donors, <40 years of age, no history of cardiac disease or cardiac risk factors, minimal inotropes and an expected warm ischemia time of 30 min. All donor hearts were perfused with the OCS Heart System. Time from withdrawal of therapy to cessation of circulation was 4–25 min (median 14 min). Total WIT was 14–28 min (median 25 min), with the time on OCS from 210–410 min (mean: 302 min). Results for 12 patients have been reported. Postoperatively, one patient needed mechanical support with intra-aortic balloon pump (IABP) and four patients required extracorporeal membrane oxygenation (ECMO) support. There has been no mortality and all patients have normal biventricular function at 25–829 days post-transplant at the time of the report. The authors concluded that excellent graft and recipient survival can be achieved from transplantation with DCD hearts using the OCS Heart System. Recently, the Sydney group have published a follow-up of their experience [8], in which they compared the outcome of 23 DCD hearts transplants (all retrieved by direct procurement then placed on the OCS) with a concurrent group of DBD heart transplants. Despite a higher requirement for mechanical circulatory support (39%) for primary graft dysfunction, overall survival for the DCD cohort was 95% at 1 month, 1 and 2 years post-transplant.

García Sáez *et al.* reported on the outcomes of two recipients with long-term left ventricular assist device (LVAD) support who were successfully transplanted with DCD hearts preserved on the OCS Heart System despite the adverse donor/recipient risk profile [9]. The authors noted, "The ability to assess graft viability is of particular importance in DCD heart transplantation, where, in contrast to the DBD setting, the donor organ has invariably been subjected to a sustained ischemic insult before procurement. We deliberately prolonged OCS support duration to allow comprehensive graft assessment and to achieve surgical preparedness in technically demanding recipients with LVADs *in situ*." In this report, the two patients were alive and well 290 and 291 days after transplantation.

In summary, studies of the OCS Heart System for the preservation of DCD hearts have been performed in UK and Australia outside of the USA. These studies have shown 77.8–86.7% utilization rate, with 90-day and 1-year

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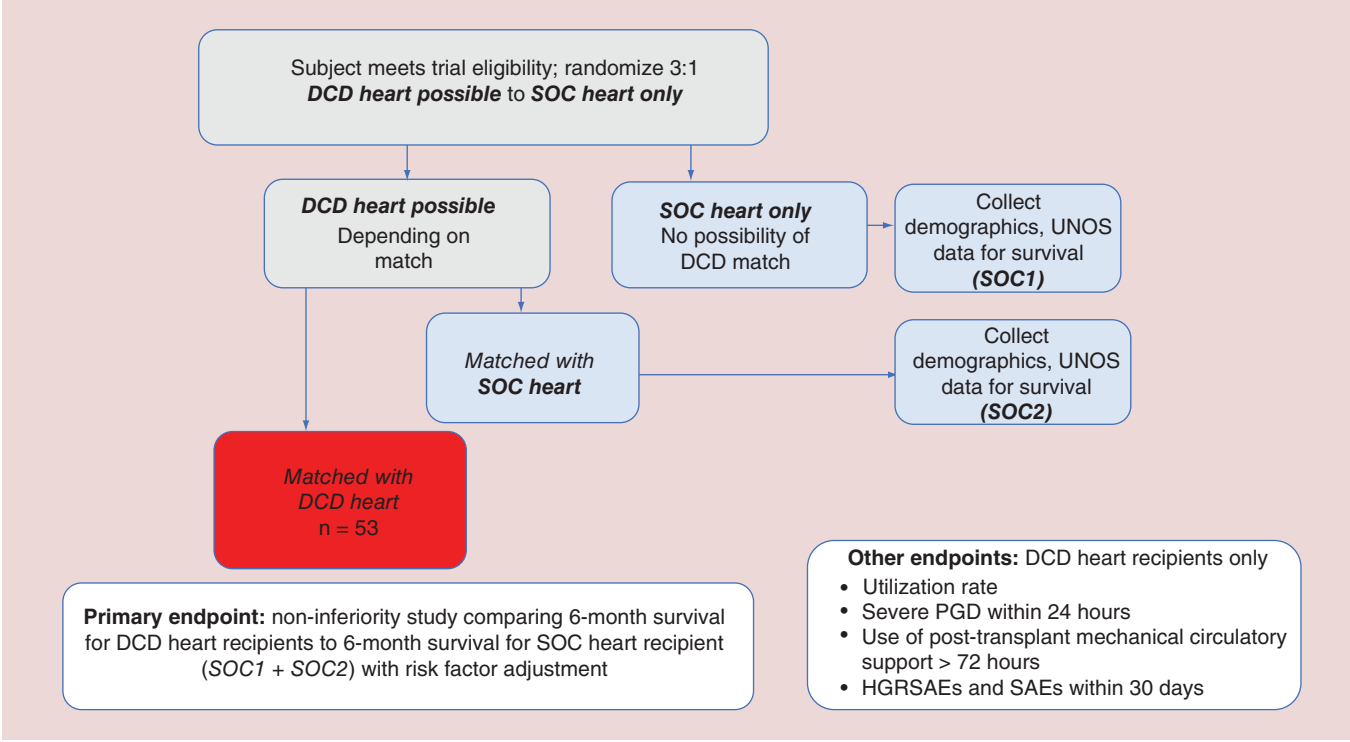

Figure 2. The trial design of the Donation after Circulatory Death Heart trial.
DCD: Donation after circulatory death; HGRSAE; Heart graft-related serious adverse events; PGD; Primary graft dysfunction; SAEs; Serious adverse events; SOC; Standard criteria donation.
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survival comparable to outcomes obtained with standard criteria donor hearts preserved using cold storage standard of care. These data provide strong support for the initiation of the DCD heart trial.

The objective of the DCD heart trial is to evaluate the effectiveness of the OCS Heart System to preserve and assess hearts donated after circulatory death for transplantation to increase the pool of donor hearts available for transplantation.

Design

Study design

A prospective, randomized and concurrent controlled, noninferiority pivotal trial in which subjects who receive a DCD donor heart transplant will be compared with subjects who receive a standard criteria donor heart transplant (SOC1 and SOC2 – from both randomized and concurrent control groups), adjusting for differences in risk factors. The trial design is illustrated in Figure 2.

Eligibility criteria

DCD donor eligibility criteria

Inclusion criteria

- Maastricht Category III DCD donor, defined as expected death after the withdrawal of life-supportive therapy;
- Donor age 18–49 years old inclusive;
- WIT ≤30 min, with WIT defined as: time from when mean systolic blood pressure is <50 mmHg or peripheral saturation <70% to aortic cross-clamp and administration of cold cardioplegia in the donor [10,11].

Exclusion criteria

Donor hearts will be excluded, if they meet any of the following criteria:

- Previous cardiac surgery;

- Known coronary artery disease;
- Cardiogenic shock or myocardial infarction, or;
- Sustained terminal ejection fraction (EF) of ≤50%, or;
- Significant valve disease except for competent bicuspid aortic valve.

Recipient eligibility criteria

Inclusion criteria

- Primary heart transplant candidates;
- Age ≥18 years old;
- Signed: written informed consent document; authorization to use and disclose protected health information; and consent to TransMedics' use of recipients' UNOS/OPTN data and consent to TransMedics' use of recipients' INTERMACS data.

Exclusion criteria

- Prior solid organ or bone marrow transplant;
- Chronic use of hemodialysis or diagnosis of chronic renal insufficiency;
- Multiorgan transplant;
- Investigator unwilling to randomize to either arm.

DCD donor heart on OCS transplant criteria

Donor hearts will be preserved on the OCS Heart System to be maintained within the following target ranges:

- Stable or downward trending lactate after an initial stabilization period;
- Stability of OCS Heart perfusion parameters within range (AOP, 40–100 mmHg).

Planned sample size

A maximum of 25 participating sites with a minimum of 53 transplanted DCD heart recipients and at least 159 standard of care heart transplant recipients.

Planned study period

Follow-up data for the SOC recipients will be obtained from UNOS/OPTN standard database for transplant recipients. Subjects who receive a DCD heart transplant will be followed for 12 months from the date of transplantation (some of which will be postmarket).

Study procedures

Primary heart transplant candidates will be screened for trial eligibility. Subjects will be randomized into two groups: DCD Heart Possible and SOC Heart Only. Subjects who are randomized into the SOC Heart Only group will have no possibility for a DCD heart transplant. Subjects randomized into the DCD Heart Possible group have the possibility of receiving either a DCD heart preserved on OCS or an SOC donor heart, depending upon the donor match. In order to obtain enough subjects with DCD donor heart transplants, subjects will be randomized 3:1 to the DCD Heart Possible and SOC Heart Only arms, respectively. Follow-up survival data for transplanted subjects in the SOC Heart Transplanted Recipient (SOC1) group will be obtained from the UNOS/OPTN standard database for transplant recipients. Upon receiving a donor heart match and after confirmation of eligibility, SOC Heart Transplanted Recipients will have demographic information collected and will then exit the study and undergo standard heart transplantation according to the institution's standard of care.

In the DCD Heart Possible arm, if a screened and eligible subject is matched with an SOC donor heart before an eligible DCD donor heart becomes available and is transplanted, these subjects will form a second SOC Heart Transplanted Recipient group (SOC2). Follow-up survival data for subjects in the SOC2 group will be obtained from the UNOS/OPTN standard database for transplant recipients. Upon receiving a donor heart match and after confirmation of eligibility, SOC Heart Transplanted Recipients will have demographic information collected and will then exit the study and undergo standard heart transplantation according to the institution's standard of care.

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Data will be collected according to this protocol for subjects in the DCD Heart Possible arm who receive a DCD heart match and are transplanted with the DCD heart as outlined in this protocol (DCD Heart Transplanted Recipient group).

Outcome measures/end points

Primary end point

A noninferiority comparison of patient survival at 6 months post-transplant between recipients of DCD donor hearts preserved on the OCS Heart System (DCD Heart Transplanted Recipient Population) and recipients of standard criteria donor hearts preserved using cold storage (SOC1 + SOC2, SOC Heart Transplanted Recipient Population), adjusting for risk factors.

Secondary end point

Utilization Rate is defined as the number of eligible DCD donor hearts that met the WIT limit and were instrumented on the OCS Heart System that meet the acceptance criteria for transplantation after OCS Heart preservation divided by the total number of eligible DCD donor hearts that met the WIT limit above and were instrumented on the OCS Heart System.

Safety

The safety end point is defined as the incidence of heart graft-related serious adverse events in the first 30-days postheart transplantation in the DCD Heart Transplanted Recipient Population, defined as:

- Moderate or severe heart primary graft dysfunction (PGD) (left or right ventricle) (not including rejection or cardiac tamponade) according to The International Society for Heart and Lung Transplantation (ISHLT) consensus manuscript [12];

This end point is calculated for the DCD Heart Transplanted Recipient Population only.

Other end points

Other end points collected for the DCD Heart Transplanted Recipient Population include:

- Patient and graft survival at 30-days post-transplant;
- Patient and graft survival at 30 days and initial hospital discharge, if later than 30 days;
- Severe PGD (left or right ventricle) (not including rejection or cardiac tamponade) according to ISHLT consensus manuscript [9];
- Use of post-transplant mechanical circulatory support (LVAD, right ventricular assist device, bi-ventricular assist device) for >72 h immediately post-transplant.

Other end points calculated for both the DCD Heart Transplanted Recipients and the SOC Heart Transplanted Recipients (SOC1 + SOC2) include:

Patient survival at 1 year after transplant (collected postapproval); comparison of DCD Heart Transplanted Recipients and SOC Heart Transplant Recipients (SOC1 + SOC2) through UNOS/OPTN database.

Statistics

The primary end point is a comparison of survival at 6 months for DCD Heart Transplanted Recipients and standard criteria Heart Transplanted Recipients (SOC1 + SOC2), adjusting for differences in risk factors. This is a noninferiority study.

Conclusion

The DCD heart trial will evaluate the effectiveness of the OCS Heart System to preserve and assess hearts donated after circulatory death for transplantation. Increasing the number of heart transplants by preserving DCD hearts with the OCS Heart System will have the potential to provide patients with end-stage heart failure with the life-saving treatment [13].

Executive summary

- Orthotopic heart transplantation is the gold standard treatment for end-stage heart failure.
- The persistent shortage of available donor organs has resulted in an ever-increasing waitlist and longer waiting periods for transplantation.
- Increasing the number of heart transplants by preserving extended criteria donors and donation after circulatory death hearts with the Organ Care System™ Heart System has the potential to provide the life-saving treatment to patients with end-stage heart failure.
- The objective of the Donation After Circulatory Death Heart Trial is to evaluate the effectiveness of the Organ Care System Heart System to preserve and assess hearts donated after circulatory death for transplantation to increase the pool of donor hearts available for transplantation.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: • of interest

1. Hunt SA, Abraham WT, Chin MH *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *Circulation* 112, e154–e235 (2005).
2. Mulligan MS, Shearon TH, Weill D, Pagani FD, Moore J, Murray S. Heart and lung transplantation in the United States, 1997–2006. *Am J. Transplant.* 8, 977–987 (2008).

• **Highlights the trends in heart and lung transplantation between 1997 and 2006.**

3. US Department of Health and Human Services. Organ procurement and transplantation network. https://optn.transplant.hrsa.gov/
4. Ardehali A, Esmailian F, Deng M *et al.* Ex-vivo perfusion of donor hearts for human transplantation (PROCEED II): a prospective, open-label, multicenter, randomised non-inferiority trial. *Lancet* 385(9987), 2577–2584 (2015).

• **Indicates that heart transplantation using donor hearts adequately preserved with the Organ Care System™ or with standard cold storage yield similar short-term clinical outcomes.**

5. Messer S, Page A, Axell R *et al.* Outcome after heart transplantation from donation after circulatory-determined death donors. *J. Heart Lung Transplant.* 36(12), 1311–1312 (2017).

• **Demonstrates that heart transplantation from donation after circulatory death heart donation provides comparable short-term outcomes to traditional donation after brain death heart transplants.**

6. TransMedics. www.transmedics.com
7. Dhital KK, Iyer A, Connellan M *et al.* Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. *Lancet* 385(9987), 2585–2591 (2015).
8. Chew HC, Iyer A, Connellan M *et al.* Outcomes of donation after circulatory death heart transplantation in Australia. *J. Am. Coll. Cardiol.* 73(12), 1447–1459 (2019).
9. García Saéz D, Bowles CT, Mohite PN *et al.* Heart transplantation after donor circulatory death in patients bridged to transplant with implantable left ventricular assist devices. *J. Heart Lung Transplant.* 35(10), 1255–1260 (2016).
10. White CW, Lillico R, Sandha J *et al.* Physiologic changes in the heart following cessation of mechanical ventilation in a porcine model of donation after circulatory death: implications for cardiac transplantation. *Am. J. Transplant* 16(3), 783–793 (2016).
11. Iyer A, Chew HC, Gao L *et al.* Pathophysiological trends during withdrawal of life support: implications for organ donation after circulatory death. *Transplantation* 100(12), 2621–2629 (2016).
12. Kobashigawa J, Zuckermann A, Macdonald P *et al.* Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J. Heart Lung Transplant.* 33, 327–340 (2014).
13. Donors After Circulatory Death Heart Trial (2019). https://clinicaltrials.gov/ct2/show/NCT03831048

10.2217/fca-2020-0070