Keynote Lecture Series

Moderate controlled hypothermia *vs.* standard ice-cold storage of cardiac allografts to expand the donor pool: insights from the GUARDIAN registry

David A. D'Alessandro[1], Andreas Zuckermann[2]

[1]Division of Cardiac Surgery, Department of Surgery, Massachusetts General Hospital, Boston, MA, USA; [2]Department for Cardiac Surgery, Medical University of Vienna, Vienna, Austria

Correspondence to: David A. D'Alessandro, MD. Division of Cardiac Surgery, Department of Surgery, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, USA. Email: DADALESSANDRO@mgh.harvard.edu.

For most of the last almost 60 years of heart transplantation, static ice storage has been the dominant means of organ preservation. This method has allowed about 4 hours of relatively safe cold ischemic time, after which the risk of graft dysfunction increases exponentially. This limitation governed our allocation system and limited our ability to explore remote and extended criteria donors. Static-controlled hypothermia was recently introduced into clinical practice, and accumulating data demonstrate superior results with preservation when compared to ice storage. This has allowed centers to increasingly consider remote and extended criteria donors. Herein, we review the available data within the Global Utilization and Registry Database for Improved Heart Preservation (GUARDIAN-Heart Registry), supporting the expanding use of controlled, static preservation.

Keywords: Cardiac transplantation; primary graft dysfunction (PGD); moderate hypothermic preservation

Submitted Apr 24, 2024. Accepted for publication Nov 15, 2024. Published online Dec 11, 2024.
doi: 10.21037/acs-2024-dcd-21
View this article at: https://dx.doi.org/10.21037/acs-2024-dcd-21

Heart transplantation remains the gold standard for the treatment of advanced heart failure. Advancements in the medical care of end-stage heart failure patients, as well as improvements in mechanical support systems, have led to a growing population of potential heart transplant recipients. The number of Americans with heart failure is predicted to exceed eight million by 2030 (1). Although the rate of transplants has been increasing in recent years, the potential candidates on the waitlist far exceed the number of available hearts. In the United States (US), changes to the organ allocation system made in October 2018 by the United Network for Organ Sharing (UNOS) were implemented to improve access to donor hearts for those with the most urgent need, and have led to an improvement in the waitlist mortality by prioritizing patient acuity across a broader geographic area (2). However, this has come at the cost of increasing travel distances and ischemic times (3). Furthermore, the rate of transplants remains limited by donor organ availability. Strategies to increase the donor pool have included the use of hepatitis C-positive donors, expanded criteria donors (4-6), and donors after circulatory death (7).

It is generally understood that heart transplant outcomes are impacted by both donor and recipient characteristics, many of which cannot be directly controlled. What can be controlled are the procurement and operative techniques used. Since the first heart transplant more than 50 years ago, advances have been made in operative techniques, preservation solutions, post-transplant patient management, and immunosuppression. However, less attention has been focused on graft preservation. Historically, standard donor heart preservation has relied on a cold flush followed by submersion in an ice-cooled preservation solution and transport in a picnic-type cooler packed with ice. This technique has provided approximately 4 hours of safe preservation, after which the risks of organ dysfunction

increase exponentially. The use of ice to store and transport organs results in uneven cooling and exposure to freezing temperatures, which can lead to damage to the myocardial tissue and cardiac conduction system (8-12). Hendry and colleagues studied the effect of ice-cold storage on canine hearts and found that when hearts were packaged in an ice cooler, rapid cooling was achieved, which resulted in myocardial temperatures dropping to under 2 ℃ within 1 hour (12). After 4 hours, the myocardial tissue dropped below 0 ℃. They used serial electron microscopy to reveal consequent changes such as cellular edema, nuclear swelling, and mitochondrial calcium deposits, which started when the tissue reached 2 ℃, with increasing severity over time. More recently, there has been a growing appreciation that temperatures below 4 ℃ provide suboptimal preservation, as extreme cold inhibits metabolic processes and mitochondrial function, which might be protective to some extent, during periods of static preservation.

The current heart and lung procurement consensus statement of the International Society of Heart and Lung Transplantation (ISHLT) is to transport donor hearts in preservation solution while maintaining a controlled environment between 5 and 10 ℃ at all times (13). They discuss the need for careful evaluation and management of the donor prior to procurement, and they also describe the technical aspects of the procurement and transport procedures. They further state that contact with ice should be avoided since freezing is an underappreciated cause of primary graft dysfunction (PGD).

PGD remains one of the most serious post-heart transplant complications, leading to an increased risk of mortality. Recent data from a single-center analysis has also suggested a link to later-term complications such as coronary allograft vasculopathy (14). Such a link, however, has not been substantiated, and this remains speculative. Increasing ischemic times is a well-described risk factor for PGD. Several years ago, Nicoara and colleagues, in a single center, studied 317 transplant recipients to evaluate the risk of PGD. In their practice of ice preservation, they found that each hour of ischemic time on ice resulted in a 1.8-fold greater risk of PGD [95% confidence interval (CI): 1.37–2.42; P<0.001] (15). Others have reported similar risks for PGD with increasing ischemic times, as high as a 5% increase for every 10 minutes of ischemic time (16). However, the 2018 UNOS organ allocation expanded the geographic availability of organs for the highest-risk patients to within 500 miles, which consequently increased the ischemic times of donor organs going to these patients (2). These same UNOS changes have also resulted in an increase in recipients with temporary mechanical support such as extracorporeal membrane oxygenation (ECMO) as a bridge to transplant, which is often considered a risk factor for poor post-transplant hospital course because this population is considered at a higher risk of wait-list mortality (17). The compounding risks of increasing ischemic time and increasing use of mechanical support at baseline have led to some concerns regarding the post-transplant risks of graft failure.

Commercially available since 2018, the SherpaPak® Cardiac Transport System (CTS) is the only Food and Drug Administration (FDA)-approved and Conformité Européene (CE)-marked static moderate hypothermic system designed to maintain the temperature of the heart in preservation solution at a consistent 4–8 ℃ throughout the transport time, despite extreme fluctuations in ambient temperatures (18-20). The SherpaPak System allows the heart to be immersed in a nested canister system surrounded by a novel, proprietary phase-change material that, once activated, remains at a constant temperature of between 4 and 8 ℃ for over 30 hours (18,19). The SherpaPak System also provides real-time temperature monitoring, location tracking, and communication among the transplant team using a Health Insurance Portability and Accountability Act (HIPAA)-compliant app that monitors the system at all times during transport (see *Figure 1*). The system is simple to use, requiring no specialized teams to manage, and a health economics analysis published has demonstrated significant post-transplant cost savings related to improved clinical outcomes (21).

The Global Utilization and Registry Database for Improved Heart Preservation (GUARDIAN-Heart Registry)

The GUARDIAN-Heart Registry is the largest, real-world registry comparing clinical outcomes following the use of the SherpaPak System and traditional ice-cold storage of hearts for transplant. The registry was previously described (22), but briefly, being established to collect information on donor and recipient variables and post-transplant data from various global centers with the goal of understanding the impact of controlled moderate static hypothermia on clinical outcomes. The study is registered on ClinicalTrials.gov (NCT04141605) and currently includes over 1,600 adult and pediatric transplants from 26 centers in the US, Austria, United Kingdom (UK), and Spain. The GUARDIAN-

Figure 1 The SherpaPak CTS. CTS, Cardiac Transport System.

Heart Registry is funded and administered by Paragonix Technologies (Waltham, MA, USA). Cases are enrolled in an approximate 1:1 ratio of SherpaPak to standard ice controls. Where centers are enrolling using SherpaPak exclusively for all heart transplants, centers enroll control cases consecutively in reverse, up to 3 years prior to study start at the center.

Registry data are collected through an online data repository (Medrio, San Francisco, CA, USA). The protocol and data collection forms are approved through each individual institution's ethics committee or institutional review board (IRB), or through the Western-Copernicus Group (WCG) IRB (Puyallup, Washington, DC, USA). Written informed consent was obtained when required. Recipients undergoing multi-organ transplants or re-transplants are excluded, and the study is designed to follow patients through 5 years post-transplant.

Hearts are procured from donors in a manner consistent with standard practice at each participating center. The selection of preservation solutions follows each institution's protocols, and the controls are packaged per institution standards. Donor heart preparation for preservation and transport in the SherpaPak System has been described previously (19). Transplant procedures and post-transplant care also adhere to institutional protocols.

Outcomes from the GUARDIAN-Heart Registry

Several publications have described the outcomes from the GUARDIAN-Heart Registry (21-25). The first multi-center publication was by Voigt and colleagues, provided an early look at the outcomes of 174 transplants. Using propensity matching to reduce the bias and confounders in the registry, they found that the use of the SherpaPak resulted in significant reductions in post-transplant mechanical circulatory support (MCS) utilization and intensive care unit (ICU) length of stay, leading to significant post-transplant cost savings (21). A larger analysis of data was published by Shudo and colleagues, who analyzed the baseline variables and post-transplant outcomes of 569 transplants, including 255 SherpaPak (SHRP group) and 314 ice controls (ICE group). Using the ISHLT consensus PGD definitions (26), the authors found that, despite significantly longer distances (by 172 nautical miles; P<0.001) and longer total ischemic time (by 24 minutes; P<0.001), the incidence of severe PGD was reduced by 47% in the SherpaPak cohort (10.2% ICE group *vs.* 5.4% SHRP group, P=0.03) (22). The authors then propensity-matched the data to account for differences in ischemic time, site, and enrollment era, and found that the advantages of the SherpaPak remained, with a 67% reduction in post-transplant severe PGD (12.0% ICE group *vs.* 4.0% SHRP group, P=0.011). Survival was similar in the two groups. In a subgroup analysis of longer ischemic times (>4 hours), the SherpaPak outcomes were once again superior, with a 79% reduction in severe PGD in the SherpaPak cohort compared to ice (18.0% ICE group *vs.* 3.7% SHRP group, P=0.011). A significant improvement in 30-day survival was also observed in this longer-ischemic time subgroup analysis (94.0% ICE group *vs.* 100% SHRP group, P=0.02).

We have recently published an expanded analysis of the GUARDIAN registry, where we reported on the outcomes of over 1,000 US adult cases transplanted between October 2015 and December 2022 at 15 US centers (25). In that analysis of 559 SherpaPak and 452 ice cases, the use of moderate hypothermic static preservation resulted in a significant reduction in the incidence of PGD compared to ice (6.6% *vs.* 10.4%, P=0.039), despite significantly longer ischemic times by 25 minutes (P<0.001). Following propensity matching by enrollment site, organ allocation

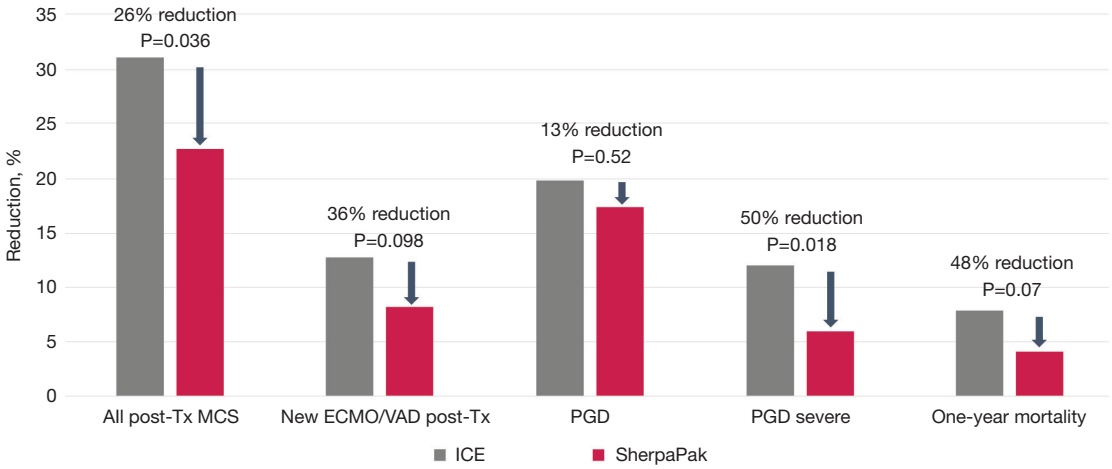

Figure 2 Post-transplant outcomes of the propensity-matched US GUARDIAN-Heart Registry population. US adult subjects (n=1,013) were propensity-matched by enrollment site, organ allocation era, ischemic time, donor age, and durable LVAD use. Outcomes reported as incidence (%), with P values calculated using the Fisher's exact test. The all MCS category includes MCS continued from pre-transplant throughout the post-transplant period. New ECMO/VAD post-transplant includes MCS use from transplant through discharge [both primary (≤24 hours) and secondary (>24 hours) graft dysfunction]. PGD severe is the use of MCS (excluding balloon pump) within 24 hours post-transplant. Tx, transplant; MCS, mechanical circulatory support; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; PGD, primary graft dysfunction; ICE, traditional ice-cold storage; US, United States; GUARDIAN-Heart Registry; Global Utilization and Registry Database for Improved Heart Preservation; LVAD, left ventricular assist device.

era, ischemic time, donor age, and durable left ventricular assist device (LVAD) use, resulting in n=281 in each cohort, severe PGD was reduced in the SherpaPak cohort compared to ice cohort by 50% (6.0% *vs.* 12.1%, P=0.018). A trend toward improved 1-year absolute survival was also noted (95.9% SHRP group *vs.* 92.1% ICE group, P=0.07) (see *Figure 2*). A hazard analysis performed to determine the impact of independent risk factors associated with donor, recipient, procedural, and transport characteristics found that use of the SherpaPak controlled hypothermic organ preservation resulted in a 39% relative lower risk of developing severe PGD compared to ice (odds ratio, 0.61; 95% CI: 0.39–0.96; P=0.032). Finally, we used logistic regression to determine the probability of severe PGD as a function of ischemic time and found that, while increasing ischemic time increased the probability of severe PGD in both the SherpaPak and ice cohorts, the risk was significantly attenuated in the SherpaPak cohort, with a P value of 0.009. Importantly, this reduced risk occurred across all time points, and there was no ischemic time where the logistic regression curves crossed (25).

The use of various bridging strategies was also assessed using moderate hypothermic preservation compared to ice in a recent GUARDIAN analysis by Silvestry *et al.* (24) While MCS bridging is commonly considered a risk factor for worse post-transplant outcomes, particularly PGD, the authors noted that the use of the SherpaPak CTS in patients bridged with MCS resulted in significantly lower rates of both severe PGD (10.2% *vs.* 6.2%, P=0.046), and moderate to severe right ventricular dysfunction (31.3% *vs.* 21.4%, P=0.004) despite significantly longer total ischemic times (3.2 *vs.* 3.6 hours, P<0.001). Univariate regression analyses revealed that the overall risk of severe PGD in MCS-bridged patients had an odds ratio that was significantly lower for SherpaPak preservation compared to ice cooler storage, and that the odds of preservation of right ventricle (RV) function was significantly improved when the SherpaPak was employed for organ transport.

Extended criteria donors in GUARDIAN-Heart Registry

While optimal donor hearts are the preferred option in transplant, the perfect donor hearts are limited, necessitating the use of an "extended criteria" donor heart. The use of older donor hearts for transplant is routine in Europe, while in the US, the use of younger donors has been the norm. However, the growing population of patients awaiting

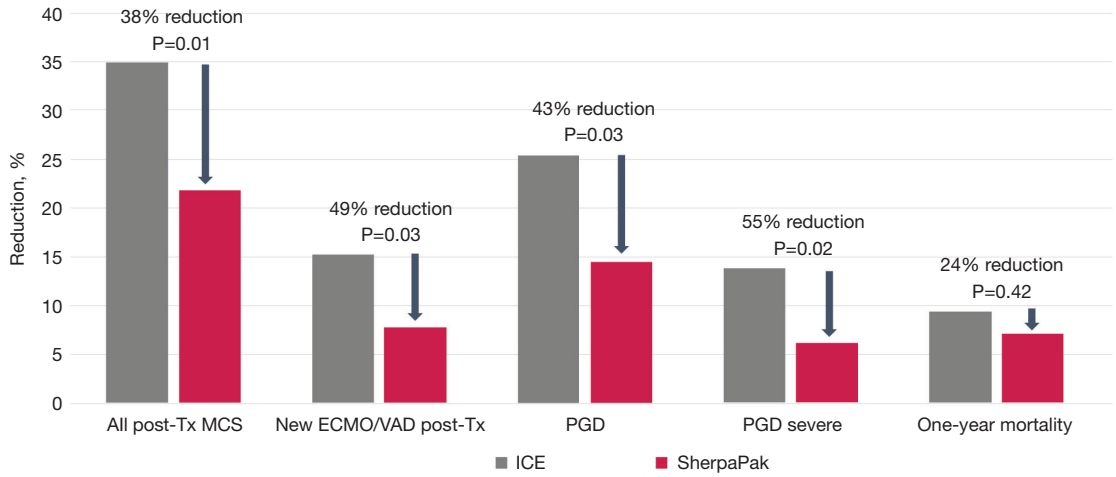

Figure 3 Post-transplant outcomes of extended criteria donors in GUARDIAN-Heart Registry. The subgroup of the US adult subjects (n=330) from the GUARDIAN-Heart Registry meeting the definition of extended criteria donors were analyzed. Outcomes reported as incidence (%), with P values calculated using the Fisher's exact test. The all MCS category includes MCS continued from pre-transplant throughout the post-transplant period. New ECMO/VAD post-transplant includes MCS use from transplant through discharge [both primary (≤24 hours) and secondary (>24 hours) graft dysfunction]. PGD severe is the use of MCS (excluding balloon pump) within 24 hours post-transplant. Tx, transplant; MCS, mechanical circulatory support; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; PGD, primary graft dysfunction; ICE, traditional ice-cold storage; US, United States; GUARDIAN-Heart Registry; Global Utilization and Registry Database for Improved Heart Preservation.

heart transplants has necessitated a reevaluation of the use of these extended criteria, including older donor hearts. Copeland and colleagues recently published donor heart selection guidelines, which reinforce the need to carefully consider the acceptable risk to the recipient when the donor heart is selected (4). The Organ Care System (OCS) EXPAND study was recently published, demonstrating that extended criteria donor hearts could be safely utilized using the OCS (27).

Moayedifar and colleagues used the criteria described in the EXPAND study to identify transplants in the GUARDIAN-Heart Registry that met these criteria, and found that just over 32% of the US adult transplants utilized donor organs meeting these definitions (23). Extended donor criteria included donor hearts with a total ischemic time of >4 hours or those with a total ischemic time of >2 hours along with at least one additional criterion, such as >55 years of age, downtime >20 minutes, left ventricular ejection fraction 40–50%, left ventricle posterior wall thickness 12–16 mm, or luminal irregularities. In that analysis of 330 transplants (193 SHRP group and 137 ICE group), SherpaPak utilization resulted in a 43% reduction in PGD (P=0.015), and a 55% reduction in severe PGD (P=0.022) when compared to hearts transported in ice (see *Figure 3*). Additionally, a logistic regression revealed that use of the SherpaPak resulted in a reduction in the odds of severe PGD by more than 60% when using extended criteria donors.

Data in the GUARDIAN registry on European transplants is not, at this point, robust and only from a few enrolling centers. Nevertheless, outcomes from these centers further support the use of the SherpaPak over ice preservation. Furthermore, results described above with extended criteria donors support the use of the SherpaPak in the European practice. With less access to donors, older donors, and prolonged ischemic times are expected and considered normal criteria. Ideally, the registry will have more global representation in the years ahead.

Preliminary outcomes in donation after circulatory death (DCD) donors in GUARDIAN-Heart Registry

While most of the current transplants entered into the GUARDIAN-Heart Registry are from donation after brain death (DBD) donors, there are some limited enrollments from DCD donors. There are currently 27 DCD cases using the SherpaPak CTS following the use

Table 1 Baseline characteristics and post-transplant outcomes in transplants using DCD hearts preserved in the SherpaPak CTS in the GUARDIAN registry

Parameters	SherpaPak CTS (n=27)
Donor characteristics	
Age (years)	32.7±8.2
BMI (kg/m^2)	31.3±7.6
Distance to organ (miles)	344±319
Total ischemic time (hours)	3.6±1.1
Average temperature (℃)	5.1±0.7
Recipient characteristics	
Age (years)	56.4±9.9
BMI (kg/m^2)	29.8±4.6
Waitlist days	184.6
Median waitlist days (min, max)	46.0 (1.0, 1,924.0)
Implantable VAD	11/27 (40.7)
Temporary IABP	4/27 (14.8)
ECMO/temporary VAD	4/27 (14.8)
Post-transplant outcomes	
Cardioversion	6/27 (22.2)
All post-Tx MCS	3/27 (11.1)
New ECMO/VAD post-Tx	2/27 (7.4)
PGD	7/27 (25.9)
PGD severe	2/27 (7.4)
RV normal (no RVD observed) at 24 hours	10/23 (43.5)
Severe RVD at 24 hours	0/23 (0.0)
LVEF % 24 hours	49.2±15.7
Inotrope score at 24 hours	12.5±5.0
ICU length of stay (days)	9.6±13.9
Total hospital LOS (days)	18.3±12.9
In-hospital survival	27/27 (100.0)

Data are presented ad mean ± SD, mean, or n/total (%), unless otherwise stated. DCD, donation after cardiac death; CTS, Cardiac Transport System; BMI, body mass index; VAD, ventricular assist device; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; Tx, transplant; MCS, mechanical circulatory support; PGD, primary graft dysfunction; RV, right ventricular; RVD, right ventricular dysfunction; LVEF, left ventricular ejection fraction; ICU, intensive care unit; LOS, length of stay; SD, standard deviation.

of thoracoabdominal normothermic regional perfusion (TA-NRP) to reinstitute thoracoabdominal blood flow following cardiac arrest. The baseline characteristics are presented in *Table 1*. The average donor age was 32.7 years old, with an average total ischemic time reported as 3.6 hours. The average recipient age was 56.4 years old, with an average waitlist time of 185 days. A total of 40.7% of recipients receiving a DCD heart were bridged with an LVAD prior to transplant. Post-transplant, severe PGD occurred in 2 recipients (7.4%), while the right ventricular function was preserved in 43.5% of recipients at 24 hours. The average total length of ICU stay was 9.6 days, and the average total hospital stay was 18.3 days. The in-hospital survival rate was 100%.

Discussion

The data from the GUARDIAN-Heart Registry suggests that the use of the SherpaPak controlled moderate hypothermic preservation system reduces the risk of adverse post-transplant events. The need to increase the availability of donor hearts is leading to the expansion of the donor criteria and the extension of previously accepted ischemic times. Data from the GUARDIAN registry demonstrates that the SherpaPak can be used in significantly longer ischemic times without negatively impacting the risk of severe PGD. Additionally, the SherpaPak attenuates the risk of using extended criteria donors when compared to ice cooler transport. While the majority of factors that have traditionally been associated with the risk of post-transplant severe PGD have been donor and recipient variables that are difficult to control, the identification of the preservation environment is one that is easily controlled through the utilization of the SherpaPak System. The use of moderate controlled hypothermia can thus expand the donor pool to longer ischemic times and extended criteria donors without sacrificing good post-transplant outcomes. Several case reports have recently been published, revealing safe use of the SherpaPak CTS for very long distances and ischemic times upwards of 7.5 hours (28,29).

The data published to date from the GUARDIAN registry has been limited to the US experience using DBD donors, including those meeting extended criteria definitions. A recent UNOS analysis has shown that the utilization of DCD hearts can decrease waitlist times without negatively impacting survival (30). However, while DCD donors tend to be younger and healthier, the hearts are exposed to increased warm ischemic injury

due to extended circulatory arrest times. Therefore, transplantation using DCD hearts generally requires preconditioning in order to mitigate injury. A method for utilization of DCD hearts after conditioning, which involves using cardiopulmonary bypass or a modified ECMO circuit for TA-NRP and subsequent transportation using cold static storage, has shown promising outcomes (31,32). The use of TA-NRP allows for *in-situ* cardiac assessment under physiologic conditions, which improves the acceptance rate and potential outcomes of the organs.

Since the use of the SherpaPak CTS has shown such significant advantages over ice cooler transport, particularly around the attenuation of the adverse effects of increased ischemic time, there is increasing interest in pairing TA-NRP followed by transport of the DCD donor heart to the recipient hospital using controlled moderate hypothermia, which avoids additional organ injury due to exposure to ice. Controlled moderate hypothermia further allows cellular functions, which could be important for cellular repair. An interrogation of the data in the GUARDIAN-Heart Registry found that there are currently 27 DCD heart transplants utilizing the SherpaPak CTS following NRP. While the numbers are still small, it is encouraging to find the in-hospital survival is 100%. It is interesting to note that the average age of the donors in the DCD cohort was 32.7 years, similar to the DBD hearts transported in the SherpaPak CTS at 32.9 years, as reported in the recent publication by us in the *Journal of Heart and Lung Transplantation* (*JHLT*) (25). The average total ischemic times were also similar, at 3.6 hours in both the DCD and DBD analyses for the SherpaPak cohorts. However, the average waitlist time in the DCD cohort was 185 days, compared to 143 days in the recipients receiving DBD hearts transported in the SherpaPak CTS. Therefore, it appears that the DBD hearts are being used in an effort to transplant recipients who are waiting longer for transplants or lower on the organ allocation listing. In fact, a review of the baseline durable VADs, who are lower on the transplant allocation listing, in each of the analyses, revealed that while 26.6% of the recipients have a durable VAD in the SherpaPak cohort in the overall published analysis, 41.7% have a durable VAD as a bridge to transplant in the DCD cohort.

While the dataset is small, these preliminary results of DCD donor hearts preserved and transported in a SherpaPak following TA-NRP are very encouraging, and are comparable to the excellent outcomes observed with the use of the SherpaPak CTS in recipients receiving hearts from DBD donors, as well as from the extended criteria donors. Continued enrollment of DCD heart transplant cases in the GUARDIAN-Heart Registry should allow for a more rigorous evaluation of the use of the SherpaPak in the DCD transplant population, as well as comparisons with other means of organ preservation. With respect to DBD heart transplantation and DBD transplants using extended criteria donors, the GUARDIAN-Heart Registry data support the use of controlled hypothermia over ice preservation.

Acknowledgments

The authors greatly acknowledge the medical writing assistance of Mary V. Jacoski of Paragonix, Inc.

Footnote

Funding: The GUARDIAN registry is fully funded and supported by Paragonix, Inc.

Conflicts of Interest: Both authors have no conflicts of interest to declare.

References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation 2023;147:e93-e621. Erratum in: Circulation 2023;147:e622. Erratum in: Circulation 2023;148:e4.
2. Siddiqi U, Lirette S, Hoang R, et al. Ischemic time and patient outcomes after the 2018 UNOS donor heart allocation system change. J Card Surg 2022;37:2685-90.
3. Maitra NS, Dugger SJ, Balachandran IC, et al. Impact of the 2018 UNOS Heart Transplant Policy Changes on Patient Outcomes. JACC Heart Fail 2023;11:491-503.
4. Copeland H, Knezevic I, Baran DA, et al. Donor heart

selection: Evidence-based guidelines for providers. J Heart Lung Transplant 2023;42:7-29.
5. Rochlani Y, Diab K, Jorde UP. Hepatitis C-Positive Donors in Cardiac Transplantation: Problems and Opportunities. Curr Heart Fail Rep 2020;17:106-15.
6. Altshuler PJ, Helmers MR, Schiazza AR, et al. HCV-Positive Allograft Use in Heart Transplantation Is Associated With Increased Access to Overdose Donors and Reduced Waitlist Mortality Without Compromising Outcomes. J Card Fail 2022;28:32-41.
7. Messer SJ, Axell RG, Colah S, et al. Functional assessment and transplantation of the donor heart after circulatory death. J Heart Lung Transplant 2016;35:1443-52.
8. Horch DF, Mehlitz T, Laurich O, et al. Organ transport temperature box: multicenter study on transport temperature of organs. Transplant Proc 2002;34:2320.
9. Michel SG, La Muraglia GM 2nd, Madariaga ML, et al. Twelve-Hour Hypothermic Machine Perfusion for Donor Heart Preservation Leads to Improved Ultrastructural Characteristics Compared to Conventional Cold Storage. Ann Transplant 2015;20:461-8.
10. Ingemansson R, Budrikis A, Bolys R, et al. Effect of temperature in long-term preservation of vascular endothelial and smooth muscle function. Ann Thorac Surg 1996;61:1413-7.
11. Leonelli FM, Pacifico A, Young JB. Frequency and significance of conduction defects early after orthotopic heart transplantation. Am J Cardiol 1994;73:175-9.
12. Hendry PJ, Walley VM, Koshal A, et al. Are temperatures attained by donor hearts during transport too cold? J Thorac Cardiovasc Surg 1989;98:517-22.
13. Copeland H, Hayanga JWA, Neyrinck A, et al. Donor heart and lung procurement: A consensus statement. J Heart Lung Transplant 2020;39:501-17.
14. Han J, Moayedi Y, Henricksen EJ, et al. Primary Graft Dysfunction Is Associated With Development of Early Cardiac Allograft Vasculopathy, but Not Other Immune-mediated Complications, After Heart Transplantation. Transplantation 2023;107:1624-9.
15. Nicoara A, Ruffin D, Cooter M, et al. Primary graft dysfunction after heart transplantation: Incidence, trends, and associated risk factors. Am J Transplant 2018;18:1461-70.
16. Smith NF, Salehi Omran S, Genuardi MV, et al. Primary Graft Dysfunction in Heart Transplant Recipients-Risk Factors and Longitudinal Outcomes. ASAIO J 2022;68:394-401.
17. Liu J, Yang BQ, Itoh A, et al. Impact of New UNOS Allocation Criteria on Heart Transplant Practices and Outcomes. Transplant Direct 2021;7:e642.
18. Michel SG, LaMuraglia Ii GM, Madariaga ML, et al. Innovative cold storage of donor organs using the Paragonix Sherpa Pak ™ devices. Heart Lung Vessel 2015;7:246-55.
19. Bitargil M, Haddad O, Pham SM, et al. Packing the donor heart: Is SherpaPak cold preservation technique safer compared to ice cold storage. Clin Transplant 2022;36:e14707.
20. Naito N, Funamoto M, Pierson RN, et al. First clinical use of a novel hypothermic storage system for a long-distance donor heart procurement. J Thorac Cardiovasc Surg 2020;159:e121-3.
21. Voigt JD, Leacche M, Copeland H, et al. Multicenter Registry Using Propensity Score Analysis to Compare a Novel Transport/Preservation System to Traditional Means on Postoperative Hospital Outcomes and Costs for Heart Transplant Patients. ASAIO J 2023;69:345-9.
22. Shudo Y, Leacche M, Copeland H, et al. A Paradigm Shift in Heart Preservation: Improved Post-transplant Outcomes in Recipients of Donor Hearts Preserved With the SherpaPak System. ASAIO J 2023;69:993-1000.
23. Moayedifar R, Shudo Y, Kawabori M, et al. Recipient Outcomes With Extended Criteria Donors Using Advanced Heart Preservation: An Analysis of the GUARDIAN-Heart Registry. J Heart Lung Transplant 2024;43:673-80.
24. Silvestry S, Leacche M, Meyer DM, et al. Outcomes in Heart Transplant Recipients by Bridge to Transplant Strategy When Using the SherpaPak Cardiac Transport System. ASAIO J 2024;70:388-95.
25. D'Alessandro D, Schroder J, Meyer DM, et al. Impact of controlled hypothermic preservation on outcomes following heart transplantation. J Heart Lung Transplant 2024;43:1153-61.
26. Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. J Heart Lung Transplant 2014;33:327-40.
27. Schroder JN, Patel CB, DeVore AD, et al. Increasing Utilization of Extended Criteria Donor Hearts for Transplantation: The OCS Heart EXPAND Trial. JACC Heart Fail 2024;12:438-47.
28. Weininger G, Choi AY, Joseph Woo Y, et al. Successful heart transplants from over 2000 miles away. J Heart Lung Transplant 2024;43:354-6.
29. Li SS, Michel E, Osho AA, et al. Transcontinental heart

transplant using SherpaPak cold static storage system. JHLT Open 2024;4:100062.
30. Ahmed HF, Kulshrestha K, Kennedy JT, et al. Donation after circulatory death significantly reduces waitlist times while not changing post-heart transplant outcomes: A United Network for Organ Sharing Analysis. J Heart Lung Transplant 2024;43:461-70.
31. Hoffman JRH, McMaster WG, Rali AS, et al. Early US experience with cardiac donation after circulatory death (DCD) using normothermic regional perfusion. J Heart Lung Transplant 2021;40:1408-18.
32. Smith DE, Kon ZN, Carillo JA, et al. Early experience with donation after circulatory death heart transplantation using normothermic regional perfusion in the United States. J Thorac Cardiovasc Surg 2022;164:557-568.e1.

Cite this article as: D'Alessandro DA, Zuckermann A. Moderate controlled hypothermia *vs.* standard ice-cold storage of cardiac allografts to expand the donor pool: insights from the GUARDIAN registry. Ann Cardiothorac Surg 2025;14(1):28-36. doi: 10.21037/acs-2024-dcd-21