# Longterm Results of Liver Transplantation From Donation After Circulatory Death

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Donation after circulatory death (DCD) liver transplantation (LT) may imply a risk for decreased graft survival, caused by posttransplantation complications such as primary nonfunction or ischemic-type biliary lesions. However, similar survival rates for DCD and donation after brain death (DBD) LT have been reported. The objective of this study is to determine the longterm outcome of DCD LT in the Eurotransplant region corrected for the Eurotransplant donor risk index (ET-DRI). Transplants performed in Belgium and the Netherlands (January 1, 2003 to December 31, 2007) in adult recipients were included. Graft failure was defined as either the date of recipient death or retransplantation whichever occurred first (death-uncensored graft survival). Mean follow-up was 7.2 years. In total, 126 DCD and 1264 DBD LTs were performed. Kaplan-Meier survival analyses showed different graft survival for DBD and DCD at 1 year (77.7% versus 74.8%, respectively; $P = 0.71$), 5 years (65.6% versus 54.4%, respectively; $P = 0.02$), and 10 years (47.3% versus 44.2%, respectively; $P = 0.55$; log-rank $P = 0.038$). Although there was an overall significant difference, the survival curves almost reach each other after 10 years, which is most likely caused by other risk factors being less in DCD livers. Patient survival was not significantly different ($P = 0.59$). Multivariate Cox regression analysis showed a hazard ratio of 1.7 ($P < 0.001$) for DCD (corrected for ET-DRI and recipient factors). First warm ischemia time (WIT), which is the time from the end of circulation until aortic cold perfusion, over 25 minutes was associated with a lower graft survival in univariate analysis of all DCD transplants ($P = 0.002$). In conclusion, DCD LT has an increased risk for diminished graft survival compared to DBD. There was no significant difference in patient survival. DCD allografts with a first WIT > 25 minutes have an increased risk for a decrease in graft survival.

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*Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; CIT, cold ischemia time; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; DRI, donor risk index; ET-DRI, Eurotransplant donor risk index; GGT, gamma-glutamyl transpeptidase; HR, hazard ratio; HTK, histidine tryptophan ketoglutarate; ITBL, ischemic-type biliary lesion; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MOF, multiorgan failure; NAS, nonanastomotic stricture; PNF, primary nonfunction; SD, standard deviation; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing; UW, University of Wisconsin; WIT, warm ischemia time.*

Donation after circulatory death (DCD) is known to be one of the most important donor risk factors for worsened outcome after liver transplantation (LT). Previous studies have reported a hazard ratio (HR) of 1.51 in the United Network for Organ Sharing (UNOS)[1] and 1.71 in Eurotransplant.[2] Posttransplant complications such as ischemic-type biliary lesions (ITBLs) and primary nonfunction (PNF) occur more often, resulting in higher retransplantation rates.[3-6] Still, similar results for grafts from controlled DCD donors compared with grafts from donation

after brain death (DBD) donors have been reported in the initial series from the Netherlands, with a higher retransplantation rate in the DCD group due to biliary problems,[7] and a large study with data from the Scientific Registry of Transplant Recipients (SRTR) investigating DCD and DBD outcomes found decreased survival for the DCD group.[8] This indicates that the use of controlled DCD donors could be a justified alternative source for livers next to DBD donors, when bearing this additional risk in mind. Some studies even reported equally good early outcomes for extended criteria DCD grafts as compared to standard DCD grafts.[9] The same conclusions came from several (recent) reports from Belgium[10-12] and the Netherlands.[7,13]

Studies investigating risk factors in DCD LT found certain donor factors, such as age, weight, cold ischemia time (CIT), and warm ischemia time (WIT) to be significantly associated with graft failure after DCD LT.[14,15] Because the DCD procedure itself leads to a certain first WIT (the time from the end of circulation until aortic cold perfusion), which is potentially harmful to the liver, only donors with few other risk factors are being evaluated, and stricter criteria for donation are used compared to DBD donors. Furthermore, patients can be selected by Model for End-Stage Liver Disease (MELD) score in order to acquire the optimal result or highest benefit.[16-18] Unfortunately, there are few studies investigating the longterm effect of DCD on outcomes after LT.

The objective of this study is to investigate the long-term outcomes for DCD LT within the Eurotransplant region and to evaluate the effect of DCD versus DBD, adjusted for the Eurotransplant donor risk index (ET-DRI) and recipient risk factors.

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# Patients and Methods

This study is a retrospective analysis of all deceased donor LTs performed in Belgium and the Netherlands for adult (≥18 years) recipients during the period from January 1, 2003 to December 31, 2007. Transplants performed in countries that did not perform DCD transplants (Austria, Croatia, Germany, Luxemburg, and Slovenia) in this data set (n = 4549) and transplants performed with liver allografts from outside Eurotransplant (n = 89) were excluded. Follow-up data of all 1390 LTs were obtained from the Eurotransplant database in March 2015, with consent of the Eurotransplant Liver Intestine Advisory Committee. All data were anonymized for transplant center and country. The study protocol received a priori approval by the appropriate institutional review committee.

## DATA SELECTION

In the study period, DCD LTs were only performed in 2 Eurotransplant countries (Belgium and the Netherlands), and therefore, only the transplants performed in these countries were used in the analysis (n = 1390). There were 98 (7.1%) missing values in the follow-up data (patients lost to follow-up). The remaining 1292 transplants were used in the survival analysis. The DRI[1] and ET-DRI[2] were calculated for all donors when all factors were available. Because race is not registered in the Eurotransplant database, all donors were regarded as reference (Caucasian) when calculating the DRI. Because "national sharing" within UNOS is different than "national sharing" within Eurotransplant, all countries, except for Germany, were regarded as 1 donor region within Eurotransplant. National sharing was considered as extraregional sharing, meaning sharing within the whole of Eurotransplant. Because of missing CITs or most recent gamma-glutamyl transpeptidase (GGT), it was not possible to calculate the DRI for 275 donors and the ET-DRI for 290 donors; these transplants were therefore not included in the analysis with DRI/ET-DRI.

## STATISTICAL ANALYSIS

Graft survival (death-uncensored) was defined as the period from the date of transplantation until the date of retransplantation or recipient death, whichever occurred first. There is no "general agreement" within the Eurotransplant region or between the

Eurotransplant member states on strategies for retransplantation, leading to a different situation for each individual transplant center. Some centers may treat biliary complications with interventions, whereas other centers may choose for a retransplantation faster.

First WIT was defined as the time from the stopping of circulation to the starting of cold organ perfusion. For the analysis of first WIT, 5 subgroups were created: <10, 10-15, 16-20, 21-25, and >25 minutes. Clinical characteristics were summarized in mean and standard deviation (SD) for continuous variables or number and percentage for categorical factors. Comparison between groups was done using chi-square (categorical factors) or Student *t* test (continuous factors). Survival analyses were performed using Kaplan-Meier survival curves, and multivariate analyses were performed using Cox regression models. For all analyses, a Wald *P* value of $P < 0.05$ was considered significant. Statistical analyses were performed with SPSS, version 23.0 (IBM, Armonk, NY).

# Results

In total, 126 DCD and 1264 DBD LTs were performed in the study period, with a mean follow-up of 7.2 years. Donor and transplant characteristics of the 2 groups are displayed in Table 1. Significant differences between DCD and DBD were lower donor age (41.2 versus 46.8 years; $P < 0.001$), less cerebrovascular accidents (CVA) in the DCD group (41% versus 59%; $P < 0.001$), no split liver in the DCD group ($P = 0.02$), mostly local and regional allocation ($P < 0.001$), and lower CIT in the DCD group (7.2 hours versus 8.9 hours; $P < 0.001$). There was a higher percentage of rescue allocation in the DCD group (26% versus 12%; $P < 0.001$), which was the only other factor with increased risk in the DCD group.

Mean DRI and ET-DRI of DCD donors were higher as compared to the DBD group: DRI, 2.0 versus 1.6 ($P < 0.001$); ET-DRI, 2.1 versus 1.7 ($P < 0.001$). When the factor DCD was excluded from the ET-DRI/DRI calculation, the mean values in the DCD group were much lower compared to the DBD group: DRI, 1.3 versus 1.6 ($P < 0.001$); ET-DRI, 1.4 versus 1.7 ($P < 0.001$).

Recipient factors are displayed in Table 1. Recipients transplanted with a DCD liver allograft were slightly older, however, not significantly ($P = 0.42$), more often male ($P = 0.02$), had a significantly lower mean MELD score (16.2 versus 19.5; $P < 0.001$), and a lower percentage of high urgent transplantation (4.8% versus 15%; $P = 0.002$). DCD allografts underwent transplantation significantly less often in retransplantation candidates (5% versus 15%; $P = 0.002$).

**TABLE 1. Donor, Transplant, and Recipient Characteristics for DBD and DCD**

| | DBD (n = 1264) | DCD (n = 126) | *P* Value |
|---|---|---|---|
| Female donor, n (%) | 597 (47) | 49 (39) | 0.07 |
| Cause of death, n (%) | | | <0.001 |
| CVA | 749 (59) | 51 (40) | |
| Trauma | 406 (32) | 38 (30) | |
| Anoxia | 61 (5) | 22 (17) | |
| Other | 48 (4) | 15 (12) | |
| Split liver, n (%) | 52 (4.1) | 0 (0) | 0.02 |
| Allocation, n (%) | | | <0.001 |
| Local | 261 (21) | 52 (41) | |
| Regional | 617 (49) | 68 (54) | |
| Extraregional | 386 (31) | 6 (5) | |
| Rescue allocation, n (%) | 157 (12) | 33 (26) | <0.001 |
| Perfusion fluid, n (%) | | | |
| UW | 614 (49) | 58 (46) | |
| HTK | 559 (44) | 58 (46) | |
| Other | 91 (7.2) | 10 (8) | 0.85 |
| Donor age, years, mean (SD) | 46.8 (15.9) | 41.2 (14.1) | <0.001 |
| Height, mean (SD) | 173 (9.5) | 175 (9.5) | 0.049 |
| BMI, mean (SD) | 24.6 (3.6) | 24.3 (3.6) | 0.47 |
| GGT, U/L, mean (SD) | 53 (82) | 50 (69) | 0.67 |
| First WIT, minutes, mean (SD) | Not available | 13.2 (7.3) | |
| CIT, hours, mean (SD) | 8.9 (2.8) | 7.2 (2.1) | <0.001 |
| DRI, mean (SD) | 1.58 (0.39) | 2.00 (0.38) | <0.001 |
| without factor DCD* | Not available | 1.33 (0.25) | |
| ET-DRI, mean (SD) | 1.65 (0.40) | 2.13 (0.43) | <0.001 |
| without factor DCD* | Not available | 1.44 (0.29) | |
| Recipient sex, n (%) | | | 0.02 |
| Male | 810 (64) | 94 (75) | |
| Female | 454 (36) | 32 (25) | |
| High urgent, n (%) | 184 (15) | 6 (4.8) | 0.002 |
| Repeated transplant, n (%) | 192 (15) | 6 (4.8) | 0.001 |
| Recipient age, years, mean (SD) | 51.6 (11.8) | 53.0 (11.5) | 0.42 |
| MELD, mean (SD) | 19.5 (9.9) | 16.2 (7.8) | 0.004 |

*Not applicable because this only applies for DCD donors; value is equal to value above (DRI, 1.58; ET-DRI, 1.65).

## LONGTERM OUTCOME OF DCD VERSUS DBD

Kaplan-Meier survival curves showed different graft survival rates for DCD versus DBD (log-rank $P = 0.038$; Fig. 1; Table 2), meaning there were more added life-years (or grafts lasted longer after transplantation) of a DBD liver compared to a DCD liver (reflected in the area under the curve). Specific graft survival at 1 (75% versus 78%; $P = 0.71$), 5 (54% versus 66%; $P = 0.02$), and 10 years (44% versus 47%; $P = 0.55$) showed that the differences in graft survival increased in the first 5

years and decreased in the following years, leveling out at approximately 10 years after transplantation.

Univariate Cox regression analysis gave a HR of 1.31 (95% confidence interval [CI], 1.01-1.69; $P = 0.04$) for DCD compared to DBD. There was no significant difference in patient survival between DCD and DBD at the previously named time points ($P = 0.59$; Table 2). Interestingly, patient death was not significantly different, but there was a significantly higher chance for retransplantation after DCD LT. Reasons for patient death or retransplantation are shown in Table 3. Thrombosis was a relatively more frequent cause of retransplantation after DBD LT (1.7% versus 0.8%), whereas the DCD recipients had a higher percentage of PNF (3.2% versus 0.7%) and nonanastomotic strictures (NASs; 6.3% versus 0.6%; $P = 0.002$).

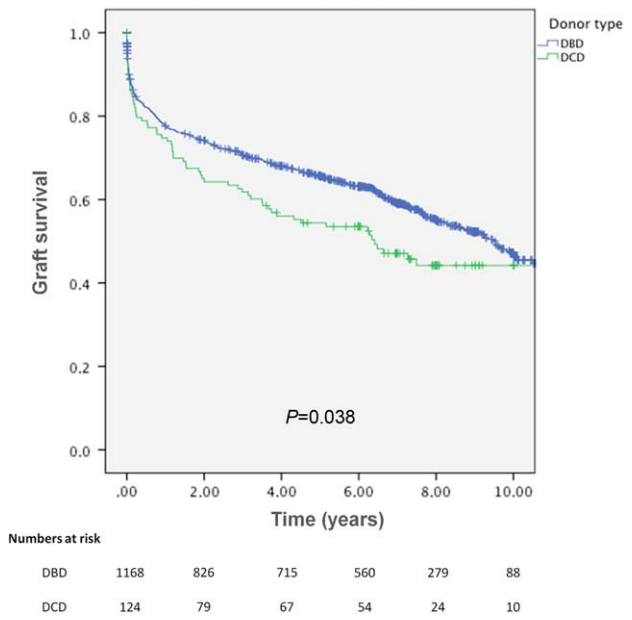


**FIG. 1.** Longterm graft survival for DCD and DBD transplantations (log-rank test $P = 0.038$). The green line shows DCD transplantations. The blue line shows DBD transplantations.

## MULTIVARIATE ANALYSIS

Multivariate Cox regression analyses of the "DCD factor" in relation to graft survival, corrected for other factors in the DRI, ET-DRI, and all available recipient factors (age, MELD, high urgent status, cause of end-stage liver disease, and retransplantation status), gave a HR of 1.86 (95% CI, 1.38-2.52; $P < 0.001$; for DRI factors) and 1.81 (95% CI, 1.33-2.47; $P < 0.001$; for ET-DRI factors), respectively. When the DCD was corrected for the calculated DRI and ET-DRI (calculated without the factor DCD) and recipient factors, it remained significantly associated with graft survival with a HR of 1.73 (95% CI, 1.30-2.30; $P < 0.001$; DRI) and 1.70 (95% CI, 1.27-2.25; $P < 0.001$; ET-DRI), respectively. This also confirms the strong correlation between the DRI, ET-DRI, and DCD.

## SUBANALYSIS OF FIRST WIT

Next, a subanalysis of the DCD group was performed (n = 126) to investigate the influence of the first WIT. Mean first WIT was 14 minutes (range, 4-38 minutes).

**TABLE 3. Causes of Death or Retransplantation for DBD and DCD LTs**

| Causes of graft loss | DBD (n = 1264) | DCD (n = 126) | *P* Value* |
|---|---|---|---|
| Death, n (%) | 424 (34) | 48 (38) | 0.83 |
| MOF/ARDS/sepsis | 79 (6.3) | 8 (6.3) | |
| Infection | 48 (3.8) | 8 (6.3) | |
| Cardiac | 31 (2.5) | 3 (2.4) | |
| Malignant | 98 (7.8) | 13 (10) | |
| Other | 115 (9.1) | 10 (7.9) | |
| Unknown | 53 (4.2) | 6 (4.8) | |
| Retransplantation, n (%) | 73 (5.8) | 18 (14) | 0.002 |
| Thrombosis | 22 (1.7) | 1 (0.8) | |
| PNF | 9 (0.7) | 4 (3.2) | |
| NAS | 7 (0.6) | 8 (6.3) | |
| Rejection | 5 (0.4) | — | |
| Other | 8 (0.6) | 3 (2.4) | |
| Unknown | 22 (1.7) | 2 (1.6) | |

**P* value of chi-square analysis of subgroups in cause of death or cause of retransplantation.

**TABLE 2. Death-Uncensored Graft Survival and Patient Survival After DBD and DCD LT**

| | | 1 Year | | 5 Years | | 10 Years | | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | % | 95% CI | % | 95% CI | % | 95% CI | *P* Value |
| Graft survival | | | | | | | | 0.038 |
| DBD | 1168 (90) | 77.7 | 75.3–80.1 | 65.6 | 62.8-68.4 | 47.3 | 43.1-51.5 | |
| DCD | 124 (10) | 74.8 | 67.0–82.6 | 54.4 | 45.4-63.4 | 44.2 | 34.6-53.8 | |
| Patient survival | | | | | | | | 0.59 |
| DBD | 1174 (90) | 82.8 | 80.6–85.0 | 71.4 | 68.6-74.2 | 52.6 | 48.4-56.8 | |
| DCD | 124 (10) | 87.8 | 81.8–93.8 | 68.1 | 59.5-76.7 | 55.9 | 45.9-65.9 | |

**TABLE 4. Kaplan-Meier Survival Analysis of WIT Categories (n = 123, $P = 0.12$)**

| WIT | n (%) | 5-Year Graft Survival | HR (95% CI) |
|---|---|---|---|
| <10 minutes | 34 (28) | 56% | Reference |
| 10-15 minutes | 40 (33) | 58% | 0.83 (0.44-1.55) |
| 16-20 minutes | 28 (23) | 61% | 0.86 (0.43-1.72) |
| 21-25 minutes | 15 (12) | 43% | 1.18 (0.52-2.70) |
| >25 minutes | 6 (5) | 17% | 2.87 (1.06-7.73) |

NOTE: There are 3 missing values out of 126 DCD transplants.

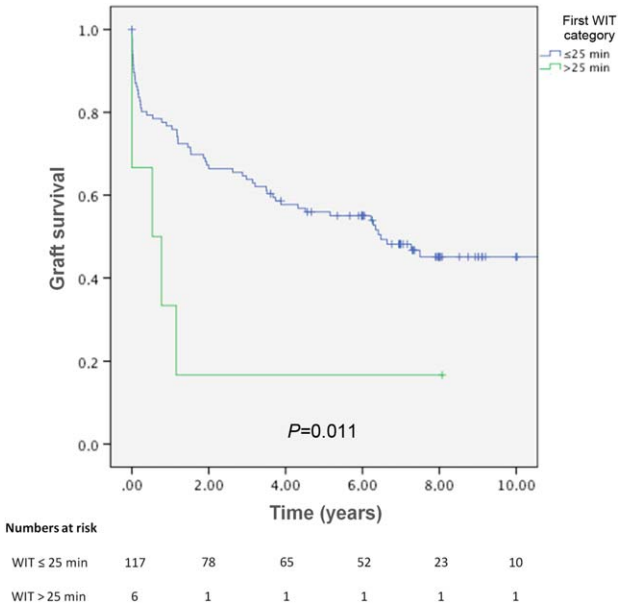


**FIG. 2.** Longterm graft survival for the first WIT categories (log-rank test $P = 0.011$). The green line shows first WIT >25 minutes. The blue line shows first WIT ≤25 minutes.

The Kaplan-Meier survival analysis of the first WIT divided into 5 categories (see Patients and Methods) was not significantly associated with graft survival (log-rank test $P = 0.12$) but showed the impact of first WIT > 25 minutes (Table 4). When performing a univariate analysis with the cutoff at 25 minutes, there was a significant correlation with graft survival (HR, 3.11; 95% CI, 1.24-7.79; $P = 0.02$). Multivariate Cox regression analysis of this factor, corrected for the ET-DRI, showed a trend toward a significant correlation with graft survival when divided into 5 categories ($P = 0.11$) and when using a cutoff of 25 minutes it was significant (HR, 3.53; 95% CI, 1.38-9.04; $P = 0.009$). Figure 2 shows the Kaplan-Meier survival curve for patients who underwent transplantation with a liver allograft that sustained >25 minutes of WIT compared with grafts with a WIT≤25 minutes.

# Discussion

This study investigated the risk of DCD LT within 2 countries belonging to the Eurotransplant region, Belgium and the Netherlands, with longterm follow-up and aimed to adjust the increased risk of the "DCD factor" by using the DRI and ET-DRI.

The results show that it seems that by adequate selection of DCD allografts, the additional risk of a DCD procedure can be kept to a minimum. This is actually a clinical practice because when excluding DCD as a factor from the DRI and ET-DRI, the risk indices became much lower for the DCD group (DRI, 1.3; ET-DRI, 1.4) as compared to the mean ET-DRI/DRI of the DBD group. This indicates that DCD donors indeed have better "other" donor characteristics, such as lower donor age, less CVAs as a cause of death, lower CIT, and no split-liver donation.

The recipient characteristics between the DBD and DCD group differed in relation to recipient MELD score, percentage of high urgency status, and repeated transplantation; DCD recipients were in better condition. The results also show that there seems to have been an increased frequency of infections in the DCD group (6.3% versus 3.8% in the DBD group). We tried to look for a possible relation with the occurrence of biliary complications, but it was impossible to extract any clear correlation from the provided data of the 11 centers.

In the Kaplan-Meier curve, graft survival at 5 years was worse in the DCD group (Fig. 1), but this difference leveled out after 10-year follow-up. Patient survival rates were not significantly different in DCD and DBD grafts at any time in follow-up (Table 2). This means that there is a higher chance for graft failure and subsequent retransplantation within the first 5 years after DCD LT, which is probably explained by the higher incidence of biliary complications (ITBL/NAS) in DCD grafts.[15,19] After 5 years, the failure risk for DCD allografts is lower when compared to DBD allografts, which might be explained in turn by the younger donor age and better condition of recipients at the time of LT. As transplant physicians take a patient's disease and current situation into account when accepting organs, they might decide to accept or decline a DCD liver allograft knowing the potential risks of this allograft after LT. Also, the consent of the patient is something that could play a role in the acceptance of such a liver allograft.

When correcting for recipient factors and ET-DRI in the multivariate analysis, DCD is a very significant

risk factor with a high hazard ratio (HR, 1.7; $P < 0.001$). This study is the first to show this additional risk by correcting for other factors that could influence outcome (donor, transplant, and recipient factors) by using the ET-DRI. A recent study by Singhal et al.[20] found similar results in a matched-controlled analysis with data from the SRTR database: DCD donors were younger, had shorter CITs, and recipients had lower MELD scores. Another finding in that study was the significantly higher associated costs and a higher readmission rate for DCD recipients, comparable to data from the Netherlands.[21] The difference in graft survival as compared to the earlier study by Dubbeld et al.[7] might be due to the acceptance of increasing risk factors when getting more acquainted with the DCD procedure over time and a larger sample size.

This study has several limitations such as the retrospective study design and the recipient selection bias because the selection was already done by the recipient centers. However, we minimized this effect by correcting for donor and recipient factors. Another limitation is the selected endpoint of combined patient and graft survival (death-uncensored graft survival) as the only outcome parameter. In order to do a good interpretation of the problems after DCD LT, biliary complications such as ITBL (or NAS) should also be taken into account as an endpoint. Unfortunately, these data are not always registered in the Eurotransplant database. Nevertheless, cases of severe biliary damage will eventually lead to retransplantation, which was taken as an endpoint in this study. Another limitation was the fact that the DRI in 275 transplants and the ET-DRI in 290 transplants could not be calculated due to missing CITs or GGT data in the Eurotransplant database. Lastly, the survival curves almost reach each other at 10 years, but the percentage of patients in the analysis at the 10-year follow-up was lower than 10% of the total number of patients in that subgroup.

The factor first WIT was demonstrated to have an important impact on the outcome of DCD LT. Donor WIT above the cutoff value of 25 minutes significantly correlated with a worse outcome ($P = 0.011$). When analyzing this factor more in detail by creating 5 different WIT groups, there was no significant correlation with graft survival, but there was clearly a lower graft survival if the first WIT exceeded 25 minutes (graft survival of 17%). Although the risk of an increased first WIT has already been described in previous studies in relation to the higher chance for PNF, graft dysfunction, or biliary strictures,[10,22] this study shows this risk after LT when correcting for the ET-DRI in the multivariate analysis. Accepting a liver graft with a first WIT above 25 minutes should probably only be considered for specific patients and only if other risk factors are minimized (donor age, CIT, etc.). Another option could be to look for strategies to decrease the risk of the first WIT exceeding 25 minutes, for example, by withdrawal of ventilatory support in the operating room as is standard protocol in Belgium. In the Netherlands, the standard procedure is to perform the withdrawal of ventilatory support in the intensive care unit (ICU). After the death is declared at the cessation of circulation, there is a mandatory no-touch period of 5 minutes, and during this period, the donor may be transported to the operating room. In Belgium, this period varies from 2 to 4 minutes,[10,23] leading to a minimal first WIT of 2-5 minutes. Practical issues, such as transport of the donor from the ICU to the operating room and preparation for organ perfusion, might lead to additional first WIT, especially in the Netherlands. Obviously, there are selected cases in which the perfusion exceeds the preferred time limit of 25 minutes, but as our results show, this only occurs incidentally. Technical issues (or lack of) do not seem to be related to these sometimes "longer" first WIT periods because all involved surgeons in the Netherlands and Belgium are specifically trained in and certified for multiorgan donation procedures.

In the Eurotransplant region, the definition of the first WIT is defined as follows: "time from cardiac arrest until perfusion of the donor."[24] This is a clear agreement made by the Eurotransplant countries. The problem is, however, that different definitions are used worldwide and that the more common definition is the time period from withdrawal of ventilation until start of cold organ perfusion. This issue has already been addressed previously.[10,23] Nevertheless, a clear and unambiguous definition remains important and should be looked at more carefully, for example, as was done by Taner et al.[25,26] in a recent UK study. Unfortunately, clinical donor data with regard to the withdrawal of life support procedures (eg, oxygen saturation or mean arterial pressure values) were not recorded in this Eurotransplant data set and could unfortunately not be investigated.

In the Netherlands, there is a strict protocol for selecting DCD donors: "the Dutch protocol for organ donation." This protocol upholds certain criteria for DCD liver allograft donation in the Netherlands, such as a maximum donor age of 60 years.[27] In 2013, the percentage of DCD LTs was 22% in Belgium and even as high as 38% in the Netherlands.[28] Although

the DCD procedure holds certain risks, such as increased rates of biliary complications, hepatic artery stenosis, or worsened outcome, it provides a valuable source for donor liver allografts in this time of organ scarcity. Univariate graft survival between the 2 groups was comparable but significantly better in the DBD group. When looking at other risk factors such as donor age and CIT for DCD donors, almost equally good results can be achieved. This was advised in the recent British Transplantation Society guidelines for DCD transplantation.[29] Nevertheless, the possibly poorer quality of life of patients with biliary strictures should also be taken into account.

The risk of DCD LT is well-known, so several measures to improve results are proposed, such as the limitation of the first WIT and CIT (which are modifiable risk factors). There is also a need to implement innovative strategies to ameliorate graft quality, such as donor preconditioning using in situ reconditioning (with the use of extracorporeal machine oxygenation) or postprocurement reconditioning by use of machine perfusion.[30] At the time of the organ offer, the first WIT is mostly not known because the DCD procedure is yet to start. After the organ recovery, the first WIT is known, and a factor that could be used to mitigate a longer first WIT is the CIT. Solutions for shortening this CIT is by local or national allocation, which is currently the case in Belgium and the Netherlands. Another factor that could correct for a potentially longer first WIT is lower donor age. As shown in this study, the ET-DRI (without the factor DCD) is significantly lower in DCD donors, with age being a major factor in the ET-DRI calculation and also being significantly lower as compared to DBD donors. Nevertheless, recent studies did not find any difference in outcome for younger or older DCD donors and concluded that a DCD donor should not be discarded purely based on age because increased donor age did not contribute to graft failure after DCD LT.[12,31]

In conclusion, this is the first European study to evaluate longterm outcome of LTs using DCD donors. DCD is confirmed to be a risk factor causing a significantly decreased graft survival after LT in Belgium and the Netherlands (HR, 1.7; $P < 0.001$). This difference in graft survival peaks at 5 years but seems to flatten out afterward. Patient survival did not significantly differ, and this should therefore encourage the use of DCD liver allografts.

Altogether, recipients of a DCD liver have a higher risk of graft loss within the first 5 years after transplantation (due to biliary complications such as ITBL), but if this is not the case, the graft survival tends to be better than with a DBD liver graft, probably because of the lower donor age and on average the better condition of the recipient at the time of transplantation. A first WIT longer than 25 minutes has a significant risk for worsened outcome after DCD LT, and when exceeding 25 minutes, the majority of transplanted DCD livers failed.

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## REFERENCES

1) Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant 2006; 6:783-790.
2) Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al.; for European Liver and Intestine Transplant Association (ELITA) and Eurotransplant Liver Intestine Advisory Committee (ELIAC). The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am J Transplant 2012;12:2789-2796.
3) Abt PL, Desai NM, Crawford MD, Forman LM, Markmann JW, Olthoff KM, Markmann JF. Survival following liver transplantation from non-heart-beating donors. Ann Surg 2004;239: 87-92.
4) Foley DP, Fernandez LA, Leverson G, Chin LT, Krieger N, Cooper JT, et al. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. Ann Surg 2005; 242:724-731.
5) Fung JJ, Eghtesad B, Patel-Tom K. Using livers from donation after cardiac death donors--a proposal to protect the true Achilles heel. Liver Transpl 2007;13:1633-1636.
6) Biggins SW, Gralla J, Dodge JL, Bambha KM, Tong S, Barón AE, et al. Survival benefit of repeat liver transplantation in the United States: a serial MELD analysis by hepatitis C status and donor risk index. Am J Transplant 2014;14:2588-2594.
7) Dubbeld J, Hoekstra H, Farid W, Ringers J, Porte RJ, Metselaar HJ, et al. Similar liver transplantation survival with selected cardiac death donors and brain death donors. Br J Surg 2010;97: 744-753.
8) Jay C, Ladner D, Wang E, Lyuksemburg V, Kang R, Chang Y, et al. A comprehensive risk assessment of mortality following donation after cardiac death liver transplant - an analysis of the national registry. J Hepatol 2011;55:808-813.
9) Tariciotti L, Rocha C, Perera MT, Gunson BK, Bramhall SR, Isaac J, et al. Is it time to extend liver acceptance criteria for controlled donors after cardiac death? Transplantation 2011;92: 1140-1146.
10) Detry O, Donckier V, Lucidi V, Ysebaert D, Chapelle T, Lerut J, et al. Liver transplantation from donation after cardiac death donors: initial Belgian experience 2003-2007. Transpl Int 2010; 23:611-618.
11) Meurisse N, Vanden Bussche S, Jochmans I, Francois J, Desschans B, Laleman W, et al. Outcomes of liver transplantations using donations after circulatory death: a single-center experience. Transplant Proc 2012;44:2868-2873.

12) Detry O, Deroover A, Meurisse N, Hans MF, Delwaide J, Lauwick S, et al. Donor age as a risk factor in donation after circulatory death liver transplantation in a controlled withdrawal protocol programme. Br J Surg 2014;101:784-792.
13) Dubbeld J, van Hoek B, Ringers J, Metselaar H, Kazemier G, van den Berg A, Porte RJ. Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcome from a single center. Ann Surg 2015;261:e64.
14) Mathur AK, Heimbach J, Steffick DE, Sonnenday CJ, Goodrich NP, Merion RM. Donation after cardiac death liver transplantation: predictors of outcome. Am J Transplant 2010;10:2512-2519.
15) Foley DP, Fernandez LA, Leverson G, Anderson M, Mezrich J, Sollinger HW, D'Alessandro A. Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. Ann Surg 2011;253:817-825.
16) Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005;5:307-313.
17) Mateo R, Cho Y, Singh G, Stapfer M, Donovan J, Kahn J, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. Am J Transplant 2006;6:791-796.
18) Merion RM, Goodrich NP, Feng S. How can we define expanded criteria for liver donors? J Hepatol 2006;45:484-488.
19) Jay CL, Lyuksemburg V, Ladner DP, Wang E, Caicedo JC, Holl JL, et al. Ischemic cholangiopathy after controlled donation after cardiac death liver transplantation: a meta-analysis. Ann Surg 2011;253:259-264.
20) Singhal A, Wima K, Hoehn RS, Quillin RC 3rd, Woodle ES, Paquette IM, et al. Hospital resource use with donation after cardiac death allografts in liver transplantation: a matched controlled analysis from 2007 to 2011. J Am Coll Surg 2015;220:951-958.
21) van der Hilst CS, Ijtsma AJ, Bottema JT, van Hoek B, Dubbeld J, Metselaar HJ, et al. The price of donation after cardiac death in liver transplantation: a prospective cost-effectiveness study. Transpl Int 2013;26:411-418.
22) Vekemans K, Monbaliu D, Balligand E, Heedfeld V, Jochmans I, Pirenne J, van Pelt J. Improving the function of liver grafts exposed to warm ischemia by the leuven drug protocol: exploring the molecular basis by microarray. Liver Transpl 2012;18:206-218.
23) Blok JJ, Braat AE, Ringers J. Reply to: asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transpl Int 2013;26:e15-e16.
24) Eurotransplant Manual. Definitions of ischemic time. Version 3.0. 2013. http://www.eurotransplant.org/cms/mediaobject.php?file=Chapter9_thedonor7.pdf.
25) Taner CB, Bulatao IG, Perry DK, Sibulesky L, Willingham DL, Kramer DJ, Nguyen JH. Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transpl Int 2012;25:838-846.
26) Burcin Taner C, Bulatao IG, Perry DK, Sibulesky L, Wllingham DL, Kramer DJ, Nguyen JH. Agonal period in donation after cardiac death donors. Transpl Int 2013;26:e17-e18.
27) Ringers J, Spreij A, Costeris N, Bokhorst AG, Braat AE, Drost G, et al. Modelprotocol postmortale orgaan- en weefseldonatie. Leiden, the Netherlands: Nerderlandse Transplantatie Stichting; 2013:1-136.
28) Rahmel AO, editor. Annual Report 2013. Eurotransplant International Foundation. Leiden, the Netherlands. 2014:1-158.
29) Andrews PA, Burnapp L, Manas D; for British Transplantation Society. Summary of the British Transplantation Society guidelines for transplantation from donors after deceased circulatory death. Transplantation 2014;97:265-270.
30) Monbaliu D, Pirenne J, Talbot D. Liver transplantation using donation after cardiac death donors. J Hepatol 2012;56:474-485.
31) Firl DJ, Hashimoto K, O'Rourke C, Diago-Uso T, Fujiki M, Aucejo FN, et al. Impact of donor age in liver transplantation from donation after circulatory death donors: a decade of experience at Cleveland Clinic. Liver Transpl 2015;21:1494-1503.