



Commentary

Time to Cast the Prejudices Towards Transplantation of Kidneys Donated After Cardiac Death?

Elisabet Van Loon^{a,b}, Line Heylen^b, Maarten Naesens^{a,b,*}^a Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium^b Department of Nephrology and Renal Transplantation, University Hospitals Leuven, Leuven, Belgium

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Renal transplantation is considered the optimal therapy for end-stage renal disease as it improves quality of life, survival and comes with reduced costs when compared to dialysis. Donor shortage however hampers the successes of kidney transplantation, and leads to large waiting lists and long waiting times. Many patients on the waiting list for kidney transplantation won't receive a graft and even die awaiting one. This pressing need for kidney donors led to extension of the donor acceptance criteria, including extended criteria grafts and grafts donated after cardiac death (DCD grafts). The use of such grafts is associated with increased early graft loss and delayed graft function (DGF). Because DGF is believed to have a negative impact on long-term graft survival, and sometimes also for ethical, religious or practical reasons, many countries and centers remain reluctant to use these types of donors. Nevertheless, the expansion of DCD transplantation leads to shorter waiting times, higher transplant rates and lower waiting list deaths [1].

Do the benefits of using DCD kidneys in terms of waiting time, transplant rates and waiting list mortality outweigh the increased risks associated with such transplantation? In the latest issue of EClinicalMedicine, Schaapherder et al. provide a large, long-term follow-up study on 6322 kidney transplantations (43% DCD), investigating the post-transplant risks of DCD kidney transplantation [2]. In the presented nationwide study built on data from a quality registry in the Netherlands, they demonstrate that there is no difference in long-term graft and recipient survival of DCD kidney transplants compared to graft donated after brain death (DBD grafts).

The Dutch registry study [2] essentially confirms data published by Summers et al. from the UK registry, which also showed equivalence in graft survival of DCD vs. DBD kidneys in a study on 7636 transplantations [3]. While the data from the UK registry could lead to discussion about generalizability (less than 10% DCD transplantation suggests potential selection bias) and differences in background transplant risk profiles between the DBD and DCD groups, this is less the case for the Dutch study. In the Netherlands, almost half of deceased donor kidneys are retrieved from cardiac dead donors, with less selection. Therefore, Schaapherder et al. [2] provide an unbiased perspective on survival of DCD kidney transplants. In addition, the Dutch registry study reports on considerably longer follow-up time (10 years after transplantation), while the study by Summers et al. only had 5 years post-transplant follow-up.

Despite the overlapping Kaplan–Meier survival curves of DCD vs. DBD kidneys in the Dutch registry study, still some differences in demographics between these groups were observed. DCD donors were more male, had less hypertension, and had a lower kidney donor risk index (when removing the DCD factor out of the equation), all favoring outcome of these DCD kidneys. Recipients of DCD kidneys were older, more male, had less HLA antibody sensitization and less repeat transplants, and were more often treated with tacrolimus compared to cyclosporine. Finally, DCD grafts were more often machine perfused than DBD kidneys. All this suggests that there is still some selection bias and/or era effects, also in this Dutch registry study [2].

To account for these differences in background risk between DCD and DBD transplantation, multivariable analyses were performed. These analyses showed a remarkable dichotomy. First, short-term outcome was significantly worse in DCD grafts compared to DBD grafts, with slightly higher risk of primary non-function (10% versus 8%) and importantly increased risk of DGF (42% versus 17%, with missing data for up to 20% of transplants). DGF on itself correlated with an increased risk of graft loss in both DBD as well as DCD grafts. Still, the multivariable analyses of this study describe equal graft survival of DCD and DBD grafts on the long term. This indicates that the increased risk of DGF in DCD kidneys did not translate in increased risk of graft failure, and thus that the impact of DGF is not the same for DCD vs. DBD grafts. This counterintuitive finding could be explained by activation of protective and repair pathophysiological mechanisms during warm ischemia in DCD kidneys, by deleterious effects of inflammatory processes

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* Corresponding author at: Department of Nephrology and Renal Transplantation, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.

E-mail address: maarten.naesens@uzleuven.be (M. Naesens).

following donor brain death in DBD grafts [4], and by the possibility that DGF in DBD kidneys primarily represents poorer graft quality, while DGF in DCD kidneys relates more to transient or less impactful ischemic injury than underlying graft quality.

The fact that DGF had less impact on long-term outcome in patients with DCD kidneys [2] is reassuring for patients and their caregivers experiencing DGF after DCD transplantation, and can take away some stress and anxiety in such clinical cases. Whether the increased risk of primary non-function of DCD transplantation should be taken into account in the context of decisions on allocation, remains however less clear. Does a significantly but slightly increased risk for early graft failure (10% vs. 8%) of DCD transplantation outweigh the risks associated with remaining on the waiting list? This question cannot be answered from the Dutch registry study.

The finding that an increased risk of DGF does not seem to translate into decreased graft survival in the study by Schaapherder et al. [2] contrasts with an earlier study also performed in the Netherlands. In that smaller study, the increased risk of DGF did translate into decreased long-term graft survival [5]. Similarly, our recent large registry study on the Eurotransplant database, on 18,065 transplants (6% DCD), which included data from the Netherlands, did demonstrate inferior outcome of DCD grafts compared to DBD grafts, with comparable long-term survival between DCD grafts and extended criteria DBD grafts [6]. Although there was a high degree of missing data/incompleteness in the Eurotransplant registry database, the discrepancies between this study and the Dutch registry analysis are puzzling and warrant more in-depth discussion.

A very important aspect in the interpretation of the study by Schaapherder et al. [2] is that DGF was included as covariate in the final multivariable model investigating the association between DCD/DBD transplantation and graft survival. With higher risk of early graft loss in DCD transplantation, it is difficult to draw firm conclusions on the overall risk of graft failure of DCD vs. DBD kidneys in this analysis adjusted for DGF, a risk factor for early graft failure. The conclusion reached by the authors however, that mid and long term outcome of DCD grafts is equivalent to outcome of DBD grafts is valid, as long as no conclusions are inferred on the short term, given that the multivariable model was adjusted for DGF as marker for short-term outcome.

A final, clinically important finding in the study by Schaapherder et al. relates to organ procurement, transport and the transplant procedure [2]. While Summers et al. found very prolonged cold ischemia times (CIT) (>24 h) to have a more profound negative impact on grafts from DCD donors compared to DBD donors [3], the Dutch registry data illustrated that the higher susceptibility of DCD grafts for cold ischemia time is limited to early graft loss, and that there was no negative impact of CIT on long-term survival. This observation could be explained by the progressive awareness and efforts to minimize cold ischemia times, indicated by the low proportion of extended CIT (>24 h) in the Dutch population. Warm anastomotic ischemia time also remained an important

target for improvement, whatever the graft type, as the impact of one-minute warm ischemia time equaled the impact of one-hour CIT for DGF in the Dutch analysis.

In conclusion, the Dutch registry study by Schaapherder et al. [2] shows that the importantly increased risk of DGF after DCD transplantation did not translate into impaired long-term outcome, while the associations between ischemia times and DGF indicate that there is room for further improvement and innovative strategies to optimize early graft function of DCD kidneys. The equal long-term outcome of DCD vs. DBD kidney transplantation could be weighed against the slightly increased risk of primary non-function. However, taken together with the high mortality risk of patients awaiting a kidney graft, abiding reluctance to massively extend the donor reservoir with DCD donors seems ungrounded.

Conflict of Interest Statement

None of the authors has a conflict of interest with regard to this publication.

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