

INVITED COMMENTARY

Improvements in Dutch heart transplant patient outcomes: lessons for the future

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Cardiac transplantation is definitive therapy for selected patients with advanced heart failure who have exhausted other options. The major limitation to expanding the number of cardiac transplants is the shortage of donor organs, and the number of heart transplant has plateaued at around 4000 per year [1]. This has led to the expansion of the utilization of mechanical circulatory support, especially in North America, parts of Europe, Japan, and Australia [1]. While survival with the newer continuous-flow ventricular assist devices is superior to that of the older pulsatile devices, cardiac transplantation is associated with the longest survival among therapies for advanced heart failure [2]. Therefore, efforts to expand the number of donor hearts would be highly desirable. Given the prevalence of MCS use, the number of hearts from marginal donors, specifically older donors, has declined, especially in the United States. While the average age of donors is in the 50s in Europe, it remains in the 30s in the United States [1]. The use of older donors up into the 50s would significantly expand the number of transplanted hearts, but the concern has been the cost in terms of post-transplant outcomes associated with the use of older donor hearts, specifically

the increased risk of developing cardiac allograft vasculopathy (CAV) [3]. The study by Zijlstra and colleagues from the Erasmus MC University Medical Center in Rotterdam in the Netherlands provides evidence for the successful, routine use of older donor hearts with outcomes superior to the earlier use of younger donor hearts and points to strategies that make this possible [4]. The authors retrospectively reviewed the clinical experiences and outcomes of their heart transplant patients during two historical periods. The first cohort was transplanted between 1984 and 1999, and the second cohort of patients was transplanted between 2000 and 2013. What demarcated these two groups was the shift in heart donors from young males who sustained brain damage from motor vehicle accidents in the older cohort to older female donors who sustained hemorrhagic strokes in the more recent patient cohort. Despite the older donors in the more recent cohort, post-transplant survival was improved in these patients as was post-transplant renal function. The authors used a more contemporary immunosuppressive regimen in the more recent patient cohort, which included tacrolimus, mycophenolate mofetil, and prednisone as opposed to

cyclosporine and prednisone in the older patient cohort. They also more aggressively treated post-transplant hypertension, which was less common in patients treated with tacrolimus. Statin therapy was initiated in all post-transplant patients regardless of their serum lipids. These results were even more remarkable given the older age and more urgent status of the recipients in the more recent cohort.

The authors attribute part of their improved outcomes in the more recent transplant patient cohort to more aggressive percutaneous therapy for CAV. Multivariate analysis indicated that myocardial revascularization with percutaneous approaches improved survival in the more recent cohort compared with the older cohort. This contention is difficult to make as the actual indication for intervening in some centers was subjective and based on qualitative assessment of the severity of CAV based on visual examination in the setting of cardiac ischemia on stress test. In other circumstances, fractional flow reserve (FFR) was used to determine the severity of CAV, and this is a more quantitative approach. Whether FFR was superior for identifying patients who would truly benefit from interventions in their CAV is not known. CAV frequency was unchanged in the more recent group compared with the older group but CAV-related sequelae such as myocardial infarctions were more common in the older group. The explanation for this appears to be the far more extensive use of statins in the more recent group (88% vs. 18% for the older group). Statins have been shown to reduce the incidence and severity of CAV and improve survival in cardiac transplant patients, and this likely had an impact on the more recent patient groups [5,6]. Further, the more intensive immunosuppressive regimen used in the more recent cohort may have mitigated the development of CAV as did the more intensive CMV prophylaxis used. How percutaneous interventions improved clinical outcomes was not clear nor was the extent of the CAV lesions, and this should be further investigated.

There are caveats to the authors' approaches to using both older donors and more intensive immunosuppression which is an increase in mortality over the first 10 years post-transplant from infection in the more recent transplant group. This did not increase the overall mortality of this group compared with the older transplant group, and the more recent transplant group had a significantly reduced overall mortality. Diabetes mellitus was also more common in the more recent transplant group and is likely a reflection of the use of tacrolimus in this patient

population. This too did not adversely affect survival in this group, and diabetes can be managed long term.

In summary, the authors responded to a precipitous decline in their usual source of heart donors who were young males in accidents using considerably older hearts predominantly from females with hemorrhagic strokes. Using a more intensive immunosuppressive regimen, more aggressive management of the recipients' hypertension, statins in as many patients as could tolerate them, and perhaps more aggressive revascularization strategies for patients with CAV, they were actually able to increase long-term survival despite the increase in deaths from infection. Their approach provides a guide for using older donors, thereby expanding the donor pool while improving survival. How this approach would work in the increasing number of patients bridged with MCS before transplant is not clear as the number of bridged patients in their populations was small, and this will need to be investigated in the future.

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