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Cardiac Transplantation in Old Heart Recipients – An Overview for those who Worry

Despite many technical advances and refined immunosuppression developed during the past decade, advanced age still remains the most controversial area in heart transplantation and is still considered a contraindication in many centers. As far as surgical and long-term results are concerned, there seems to be no difference between younger and older heart recipients. However limited number of the donors brings in the ethic concerns of using this scarce public resource for relatively unproductive elder patients. This dilemma can only be solved with each country and each center decision based on their patient and donor profiles.

Key words:

cardiac transplantation, recipient, donor, old patient

Herztransplantation bei alten Transplantatempfängern – ein Überblick zur Klärung von Bedenken

Trotz der zahlreichen in den vergangenen 10 Jahren entwickelten technischen Fortschritte und ausgefeilten immunsuppressiven Strategien bleibt das fortgeschrittene Alter nach wie vor der umstrittenste Bereich in der Herztransplantation und wird immer noch in vielen Zentren als Kontraindikation angesehen. Was chirurgische und langfristige Ergebnisse anbelangt, so scheint es keinen Unterschied zwischen jüngeren und älteren Herztransplantatempfängern zu geben. Die begrenzte Anzahl von Spendern ruft jedoch ethisch begründete Bedenken hervor, diese spärliche öffentliche Ressource für relativ unproduktive ältere Patienten zu verwenden. Dieses Dilemma kann nur gelöst werden, wenn jedes Land und jedes Zentrum seine Entscheidung auf Grundlage der Patienten- und Spenderprofile trifft.

Schlüsselwörter:

Herztransplantation, Empfänger, Spender, alter Patient

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List of Abbreviations

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ISHLT International Society for Heart and Lung Transplantation
NS non-significant
ICU Intensive Care Unit
CMV Cytomegalovirus

TCAD Transplantation Coronary Artery Disease
PTLD Post-transplant Lymphoproliferative Disorder
NYHA New York Heart Association

Introduction

With the increased life expectancy of the American population over the past few decades, elderly persons are becoming the fastest growing segment of the US population. The mean estimated life expectancy was 75.6 years in 1990 and is projected to increase further. The average American who reaches 65 years of age will live into his or her ninth decade [1]. These demographic changes are reflected in the present-day cardiac surgery practice, with an increased number of elderly individuals in need of highly sophisticated and complex cardiac interventions, including transplantation.

Heart transplantation has developed into a highly successful therapeutic option for patients with end-stage cardiomyopathy. This is reflected by an actuarial survival of 80% at 1 year and 78% at 3 years for those patients who have undergone transplantation since 1988, as reported by the International Society for Heart and Lung Transplantation [2]. Initially, heart transplantation was restricted to patients younger than 50 years of age. [3] After 1981, when cyclosporine was introduced, survival after heart transplantation progressively improved, and recipient selection criteria became less restrictive. In 2002, 2154 cardiac transplantations were performed in US and 50% of these cases were between the ages of 50-64 years.

Despite many technologic advances and more refined and specific immunosuppression developed during the past decade, advanced age remains "the last frontier" in heart transplantation and is still considered a contraindication in many centers. Support for criteria relaxation came mostly from small single-center studies describing equivalent short-term survival, as well as lower rejection rates, in older recipients [4-7]. However, other authors have reported reduced survival after transplantation in patients older than 60 years [8]. Moreover, the Registry of the International Society for Heart and Lung Transplantation (ISHLT) is still reporting increasing recipient age as a strong risk factor that adversely affects 1- and 5-year survival after heart transplantation [9].

The reports for cardiac transplantation are increasing in the literature every day, but in many instances, the results are far from being conclusive. There are

still many issues to be clarified and many more studies are needed.

Perioperative Results

Early Mortality: In a report from Blanche et al. the 30-day operative mortality was 2.5% (1/40 patients) in the older group and 2.2% (3/138 patients) in the younger group ($p = \text{NS}$) [10]. The 30-day or to-discharge operative mortality was similar in both groups (0% in the older vs 5.1% in younger patients) ($p=1.0$) [11]. Thirty-day mortality was 6% (5/81) in the patients aged 60 years and older and 6% (25/403) in the younger patients ($p = \text{NS}$) [12]. The only significant independent determinants of early death (<90 days) were female donor, previous sternotomy, and preoperative support with inotropes. Increasing recipient age was not identified as an independent risk factor for early and late death [12].

Acute Rejection: Reports for acute rejection show similar results in younger and older patient groups. In the report by Blanche et al., the incidence of rejection during the first post-transplant year was similar in both groups, with a mean number of rejection episodes of 0.8 per patient for the patients over 65 years old and 0.9 per patient for the younger group ($p = 0.45$) [10]. A low incidence of rejection (one episode of IB rejection in 1 patient) has also been documented by Blanche in a different report [13]. The incidence of rejection episodes was similar in both groups, with a mean number of rejection episodes of 0.13 ± 0.35 per patient in the older group and 0.24 ± 0.5 per patient in the younger group ($P = 0.77$) [10]. In the report of Demers et al., patients aged 60 years and older had lower rejection episodes compared to younger age groups. In patients over 60 years old, 2.0 ± 1.1 acute allograft rejection episodes per patient were met, compared with 2.6 ± 1.8 episodes per patient in younger recipients, and the difference was statistically significant ($P = 0.003$). Moreover, actuarial freedom from acute rejection at 3 months, 1 year, and 2 years was significantly higher in older patients ($49\% \pm 6\%$ vs. $33\% \pm 2\%$, $39\% \pm 6\%$ vs. $27\% \pm 2\%$, and $36\% \pm 6\%$ vs. $24\% \pm 2\%$; $P = .01$) [12].

In a recent article by Morgan et al., the most common ISHLT grade of rejection was 1A, occurring in 43 (68.3%) patients in the older group and 47 (74.6%) patients in the younger group [14].

ICU and Hospital Stay: The post-transplant intensive care unit stay and total hospital stay were similar in both groups, which translated into similar total hospital costs [10]. A comparative analysis of the intensive care unit and post-transplant hospital stays between hospital survivors among the younger patients (14 to 69.9 years old) and the septuagenarians (70 to 77 years old) are similar for the two groups of patients, but the small sample size of the septuagenarians does not allow for any statistical validation [13]. The length of intensive care unit stay and total post-transplantation hospital stay, incidence of rejection, and incidence of cytomegalovirus infection were similar between the groups [11]. Mean hospital stay was similar in both groups [12]. Postoperative length of stay in the intensive care unit was not statistically different between the older and younger groups (8.8 ± 9.5 days versus 7.1 ± 4.7 days, respectively; $p = 0.236$). Overall hospital length of stay postoperatively was also similar (24.1 ± 17.1 days for the older group versus 23.4 ± 16.6 days for the younger group; $p = 0.837$) [14].

Infection: At the present time, no conclusions can be drawn regarding morbidity related to infection episodes [10]. A low incidence of infection (one episode of cytomegalovirus infection in a seronegative patient who received a seropositive allograft) has also been documented by Blanche in a different report [13]. The incidence of CMV infection was similar in both groups, with a mean number of CMV infection episodes of 0.14 ± 0.36 for the older group and 0.26 ± 0.5 for the younger group ($P = 1.0$) [11]. Actuarial freedom from any infection at 3 months and 1, 5, and 10 years after transplantation was not significantly different between older and younger patients. Moreover, freedom from cytomegalovirus infection at 3 months and 1, 5, and 10 years was also similar in both groups [12]. There was no difference in overall freedom from severe infection (74.1 vs. 67.7 vs. 85.3%) [12]. The incidence of infection was higher in the older group although the difference was not statistically sig-

nificant. The mean number of infections per patient was 0.25 ± 0.34 in the older group compared with 0.10 ± 0.27 in the younger group ($p = 0.135$). Freedom from infection at 1, 3, and 5 years was 88.7%, 56.0%, and 36.2%, respectively, for the older group as compared with 98.0%, 74.8%, and 49.7% for the younger group ($p = 0.406$) [14].

Allograft Coronary Artery Disease:

At the present time, no conclusions can be drawn regarding morbidity related to the incidence of transplant atherosclerosis as assessed by coronary angiography [10]. Nonspecific allograft dysfunction without allograft coronary artery vasculopathy was the cause of death in 2 elderly patients at 18 and 42 months after transplantation [11]. Actuarial freedom from allograft coronary artery disease at 1, 5, and 10 years was $98\% \pm 2\%$ versus $92\% \pm 2\%$, $85\% \pm 6\%$ versus $76\% \pm 3\%$, and $81\% \pm 7\%$ versus $68\% \pm 3\%$ in older and younger patients, respectively, a difference that failed to reach statistical significance ($P = .1$) [12]. In the series of Morgan et al., freedom from transplant coronary artery disease (TCAD) at 1, 3, and 5 years was 79.3%, 44.6%, and 31.0%, respectively, for the older group as compared with 93.0%, 72.6%, and 44.2% for the younger group ($p = 0.025$). Diagnosis of TCAD occurred at a median number of days of 985.5 for the older group and 1715.5 for the younger group ($p = 0.026$) [14].

Post-transplant Lymphoproliferative Disorder and other Cancer:

Actuarial freedom from post-transplant lymphoproliferative disorder (PTLD) 1, 5, and 10 years after transplantation was $97\% \pm 2\%$ versus $99\% \pm 1\%$, $97\% \pm 2\%$ versus $97\% \pm 1\%$, and $97\% \pm 2\%$ versus $93\% \pm 2\%$ in older and younger recipients, respectively ($P = \text{NS}$). Actuarial freedom from non-PTLD cancer at 1, 5, and 10 years was $92\% \pm 3\%$ versus $99\% \pm 1\%$, $76\% \pm 6\%$ versus $89\% \pm 2\%$, and $68\% \pm 9\%$ versus $80\% \pm 3\%$ in the older and younger patients, respectively, a difference that was statistically significant ($P = .002$) [12].

Survival: Blanche reported similar actuarial survival rates between older and younger patients [10]. Actuarial survival at 12, 24, and 36 months was not statistically different between the older and younger patients ($86\% \pm 6\%$ versus $93\% \pm 2\%$, $78\% \pm 8\%$ versus $89\% \pm$

3% , and $72\% \pm 9\%$ versus $81\% \pm 4\%$, respectively; $p = 0.26$) [10]. Similarly, actuarial survival at 1 year and 4 years was not statistically different between the older and younger patients ($93.3\% \pm 6.4\%$ vs. $88.3\% \pm 3.3\%$ and $73.5\% \pm 13.6\%$ vs. $69.1\% \pm 5.8\%$, respectively) [11]. Actuarial survival estimates at 1, 5, and 10 years for all patients were $84\% \pm 2\%$, $70\% \pm 2\%$, and $51\% \pm 3\%$, respectively. Actuarial survival at 1, 5, and 10 years was not statistically different between patients older than 60 years and patients younger than 60 years ($88\% \pm 4\%$ vs. $83\% \pm 2\%$, $75\% \pm 5\%$ vs. $73\% \pm 2\%$, and $50\% \pm 9\%$ vs $51\% \pm 3\%$, respectively) in a different series [12]. Ten year survival was similar in all groups (<60 years: 53.7%; 60-64 years: 53.1% and >65 years: 60.2%; $p = \text{NS}$) [15]. These results were parallel with the results of the series of Morgans et al. There was no significant difference in overall survival between the groups, with median survival of 9.0 years for the older group and 10.4 years for the younger group ($p = 0.597$). Actuarial survival at 1, 3, 5, and 10 years was 85.8%, 80.3%, 73.1%, and 49.9%, respectively, for the older group; and 86.9%, 83.4%, 75.0%, and 57.0%, respectively, for the younger group [14].

Discussion

Heart transplantation is the best treatment option for selected patients with end-stage heart failure who have failed medical therapy and are not amenable to other treatment options. Because of the critical shortage of donor organs, selection of candidates for transplantation is based on the potential for maximal benefit in terms of functional recovery and long-term survival. The upper age limit used to select potential candidates for heart transplantation has significantly changed over the last 20 years, and it is still a matter of debate. According to the 2000 Report from the Registry of the International Society for Heart and Lung Transplantation, increasing recipient age remains an independent risk factor that adversely affects 1- and 5-year survival after heart transplantation, with a progressive increase in risk when recipient age is greater than 55 years [9]. Initially, heart transplantation was restricted to patients younger than 50

years [3,9]. Later, as short- and long-term survival after transplantation improved, selection criteria, including age, were progressively liberalized in most heart transplantation programs. Evidence for such change in upper age limit came from several studies reporting that morbidity and mortality after heart transplantation were not significantly increased in selected older patients [4-7]. These initial reports were limited by small numbers of patients and short-term follow-up. However, other authors have subsequently reported that, survival after heart transplantation in patients older than 60 years was significantly reduced, with an increase in the incidence of life-threatening infectious complications and malignancies [8]. Interestingly, most of these early studies also suggested that patients older than 60 years had fewer acute rejection episodes after transplantation and it was postulated that older recipients, having decreased immune reactivity and reduced T-cell function, might require less immunosuppression [4-8]. Decreased immune reactivity and increased susceptibility of the elderly patients to the effects of immunosuppressive regimens have also been proposed to explain the higher incidence of infectious complications and malignancies after transplantation [8].

Heart transplantation in older patients may have the advantage of an age-associated decrease in allograft rejection without a concomitant increase in opportunistic infections [16]. Aging is associated with a generalized decline in immunologic function, particularly T-effector cell-mediated immunity. Because most cardiac allograft rejection episodes are T-cell-mediated, a decreased incidence of rejection has been observed in older patients, particularly when the dose of maintenance steroids is minimized in immunosuppression protocols [7,8,16]. Thus, older patients may require less immunosuppression than younger patients. It is perhaps this intriguing aspect of cardiac transplantation that is indirectly responsible for the increased incidence of infection cited in some reports: Elderly patients maintained on the same immunosuppression protocol as younger patients may be more susceptible to opportunistic infections if the immunosuppression regimen is not tailored to accommodate their decreased immune responsiveness.

At Stanford University, heart transplantation was offered to selected patients aged 60 years and older starting in 1986 if these patients were otherwise acceptable candidates for transplantation by using the same selection criteria as in younger candidates [12]. These recipients were listed on the regular UNOS waiting list, and allocation of donor organs was made according to UNOS status and waiting time. No effort was made to match older or so-called marginal donor hearts with older recipients. Immunosuppression protocol, infection prophylaxis, postoperative management, and monitoring of rejection were the same in the older patients. Older and younger patients were well matched for almost all pretransplant recipient characteristics and donor characteristics, except previous operation, which was more frequent in the former, and waiting time, which was longer in the older recipients. Despite these differences in baseline characteristics, they found that perioperative mortality and hospital length of stay were comparable in both groups. Multivariable analysis revealed that age at transplantation was not an independent predictor of early death. Previous sternotomy, use of a female donor, and inotropic support at the time of transplantation were the only independent risk factors for early death identified. Moreover, long-term survival after transplantation was similar in the two groups. Similarly, age at transplantation was not identified in the multivariable analysis as an independent risk factor for late death [12]. These results are consistent with those of previously discussed series [5-7, 17,18]. As reported by several authors, [5-8] the incidence of acute rejection was lower in the older patients. Although not statistically significant, the incidence of allograft coronary artery disease was also lower in the patients older than 60 years [12]. Contrary to the results of some previous reports, [7,8,19] Demers et al. did not find any difference in the incidence of infectious complications and cytomegalovirus infection in the 2 groups. However, even if the incidence of PTLD was similar in the younger and older patients, the incidence of non-PTLD cancer was significantly higher in the patients aged 60 years and older. Despite this finding, the proportion of death caused by cancer was comparable in both groups [12].

Increasing age is a known risk factor for posttransplant malignancies, and the importance of a thorough screening program in the pretransplant evaluation of older candidates and those with pre-existing malignancies has already been demonstrated [8]. Taken together, these findings suggest that patients older than 60 years might benefit from more stringently tailored immunosuppression regimens [12].

On the basis of these findings, it is easy to understand why the results of heart transplantation in the elderly can vary between transplant centers. More recently, Borkon and colleagues reported that age greater than 55 years at the time of transplantation was an independent risk factor for late death in their contemporary series of 153 heart transplant recipients, with an estimated 5-year survival of 56% in these patients compared with 78% in patients younger than 55 years [19]. These authors also observed a greater incidence of life-threatening infections in older recipients, with the same incidence of acute rejection in younger and older patients. These results were not confirmed by other recent reports [17,18]. Baron and coworkers reported their results in a series of 70 patients aged between 60 and 65 years transplanted over a period of 11 years and noted similar survival in these patients and in patients younger than 60 years transplanted during the same period, without any difference between these 2 groups in the incidence of infection and malignancy after transplantation [17]. These results are supported by data from the Registry of the International Society for Heart and Lung Transplantation. In addition, data from the ISHLT Registry show a significant decrease in survival in patients older than 65 years at 12, 24, and 36 months after heart transplantation [2]. Other studies have also shown decreased survival, increased morbidity and incidence of infection, and decreased functional capacity in older patients after heart transplantation [6-8]. Several studies have shown that heart transplantation in older patients (defined as older than 55 to 65 years of age) can be performed successfully with acceptable morbidity and mortality and excellent long-term survival, comparable with those of younger patients. These reports have concluded that the recipient's age is not a significant risk factor for mortality, and advanced age,

although its definition is not uniform, should not be considered a major contraindication for heart transplantation [17-24]. In fact, the mean age of heart transplant recipients has increased steadily within the past decade, with the number of patients 65 years of age undergoing transplantation increasing from 1.4% (n = 24) in 1988 to 8.8% (n = 206) in 1998 [25]. 203 patients (total=882) above 60 years have been transplanted by Zuckermann and colleagues and 66 of these patients were above 65 years. Old recipients of cardiac transplants have a similar long-term outcome than younger recipients. They were less prone to rejections, had a similar incidence of severe infections and showed a trend towards more CMV disease. All patients had a very low rate graft arteriosclerosis that was similar amongst the groups. Age-related decline of the immune system further enhanced by immunomodulation of antibody induction therapy might be accounted for the results as well as steroid-free immunosuppression [15]. Currently, the upper age limit for heart transplantation remains undefined, although according to available data, most transplant centers consider 65 years of age a significant risk factor that determines eligibility for transplantation [11]. In addition, an aggressive approach regarding the use of potentially compromised or "suboptimal" allografts has been used in these elderly patients with excellent clinical results, as previously documented [26,27]. The number of cardiac transplantations performed in our country remains low, compared to other organ transplantations, and the efforts of health care workers to overcome this problem remain fruitless. On this aspect, when elderly cardiac transplantation candidates are considered, the ethical issues put a lot more burden on the utilization of the very scarce cardiac donors. On the other hand, socio-economic factors also have a restraining effect for heart transplantation in the elderly. In our country, even though the life expectancy is continuously getting better, the majority of the population and the mean age of the inhabitants is still very young, as it is in any other third world country. In the last five years, 24 cardiac transplantations were performed in our center and five of these recipients were older than 55 years. One was lost in the early postoperative period due to

right heart failure, and another patient died at 3rd postoperative month due to aspergillus pneumonia. Surviving three patients are in NYHA Class I at 70th, 68th and 38th postoperative months respectively. We have not met any other early or late onset postoperative complications such as rejection, lymphoproliferative or dermatologic malignancies, renal failure or allograft vasculopathy. This picture for our center actually is a snapshot of other centers in our country or other countries that have same kind of population based ethical and socio-economical issues to be dealt, when cardiac transplantation in the elderly is the matter of discussion.

However, despite meeting all criteria, older recipients have been traditionally denied transplantation because of the critical shortage of donor organs and because of the assumption that selection for heart transplantation should be based on patient potential for maximum benefit in terms of functional recovery and length of survival. It has been argued that older patients have a postoperative period characterized by higher infection rate, higher incidence of malignant disease, greater functional impairment, increased postoperative hospital stay and associated costs, and poorer survival [6-8,19,20].

Several lessons were learned from initial experience, which remain valid over time;

1. First, the acceptance criteria for cardiac transplantation candidates at this age should be very selective to avert postoperative complications that may not be easily tolerated by older people on immunosuppressive drugs and that would therefore severely affect survival and cost [11].
2. The criteria for acceptance have been modified so that septuagenarians are only listed for transplantation as status II to minimize perioperative morbidity. Current practice is not to upgrade these patients to status I if they suffer hemodynamic deterioration. The use of mechanical support or assist devices, or both, as a bridge to transplantation in elderly patients is probably not warranted because they may not be able to tolerate the related complications. If temporary intravenous inotropic support is needed to stabilize cardiac function, their status on the transplant list

remains unchanged so that they are not "jumped ahead" of younger patients waiting for transplantation. This group of patients relies on organs deemed unsuitable by other transplant centers on the basis of the donor's weight, a lack of available recipients because of the donor's blood type, or high-risk donors with potentially compromised organs [11].

3. It is clear to us that carefully selected patients can withstand the rigors of transplantation and related protocols, have a cost-effective outcome, achieve an excellent functional result and quality of life, return to an independent lifestyle, and continue to be productive in society [11].
4. Although a purely observed phenomenon, a decreased incidence of rejection without a concomitant increase in serious infections has been noticed in these patients. This intriguing aspect of cardiac transplantation in older recipients has been previously reported and, presumably, is a manifestation of decreased immunologic function related to a decline in T-cell function [16]. Such an age-associated decrease in allograft rejection may represent an advantage for elderly individuals who undergo transplantation, which makes this approach increasingly attractive. Immunosuppressive protocols should be tailored to accommodate this decreased immune responsiveness to minimize the incidence of malignant and infectious complications [11].
5. Experience with "borderline" or potentially compromised cardiac allografts indicates that the selective use of marginally acceptable organs is compatible with excellent cardiac function and survival [26,27]. This aggressive approach of liberalizing the criteria of acceptability for donor hearts could alleviate the donor shortage in cardiac transplantation by increasing the number of available organs. However, extending the age limit of potential candidates for heart transplantation into the seventies would certainly increase the demand for organ donors and affect even further the supply-demand donor heart mismatch. This increased demand

placed on an already fixed donor pool could increase the waiting time and mortality in younger patients needing a donor heart, which in turn may raise additional moral questions and concerns [11].

6. As the indications for transplantation constantly evolve and the results in selected septuagenarians undergoing transplantation yield satisfactory results, the reasons to justify the use of marginally acceptable or "borderline" donor organs rather than "regular" allografts in elderly patients are becoming less clear. The use of an "alternate list" [28] seems also to discriminate against these patients solely on the basis of their age. The concept of matching high-risk donors with an elderly patient population that may already be at high risk may serve to expand the donor pool without compromising the lower risk and younger candidates. However, this may artificially produce a lower survival in the older patients, thus perpetuating the idea that advanced age implies less than satisfactory results [11].
7. Special attention should be given to the common problems associated with elderly patients, such as steroid-related osteoporosis, particularly during the early months of transplantation. In addition, intense rehabilitation and nutritional counseling should be provided to hasten functional recovery. In the late follow-up period, close surveillance of renal and hepatic function, as well as a psychological profile, is needed to detect behavioral changes such as depression that may change the ultimate outlook for adequate functional recovery [11].
8. The presence of strong family support with total and unrestricted commitment to the patient's well-being is essential, perhaps more so than in younger patients. Although most of these elderly patients do not carry an active full-time job, a high degree of personal and familial satisfaction can be obtained with hobby-oriented activities and easy noncompetitive sports, which in turn may produce a more positive outlook in life [11].

In summary, preliminary experience with heart transplantation in selected patients 70 years of age and older is encouraging and indicates that advanced age per se (as defined in this report) is not a contraindication to heart transplantation. However, care must be taken not to interpret these data as an endorsement to pursue this treatment modality in all septuagenarians who may be candidates for heart transplantation. Instead, highly selective criteria should be applied, identifying risks and benefits individually. The medical and socioeconomic implications are complex and the decisions involving the use of available resources and technology in a cost-effective fashion can only be made with increased knowledge regarding the unique issues associated with elderly patients [11]. Finally, our criteria for selecting potential candidates for heart transplantation have evolved so that we evaluate all potential recipients, including select septuagenarians, and identify the risks and benefits in an individual fashion.

Physicians in the future will be pressured to evaluate an increasing number of elderly patients for cardiac transplantation in light of the excellent results obtained in younger patients. Although further studies involving more patients and longer follow-up periods are needed to establish firm recommendations, these early results are encouraging. It is recommended that transplant programs carefully explore the benefits of age-related boundaries in cardiac transplantation and consider older patients, including select septuagenarians, for heart transplantation. This flexible approach would need the establishment of "alternative lists" in organ procurement programs for these older patients so that the already scarce donor organs would not be shifted away from younger recipients. These bioethical concerns are important, as controversial as they may seem [11].

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