# Extended Pancreas Donor Program—The EXPAND Study: A Prospective Multicenter Trial Testing the Use of Pancreas Donors Older Than 50 Years

Andrea Proneth, MD,[1] Andreas A. Schnitzbauer, MD,[1,2] Peter Schenker, MD,[3] Andreas Wunsch, MD,[3] Falk Rauchfuss, MD,[4] Helmut Arbogast, MD,[5] Steffen Manekeller, MD,[6] Silvio Nadalin, MD,[7] Michael Heise, MD,[8] Michael A. Ströhlein, MD,[9] Bernhard Banas, MD,[10] Peter Schemmer, MD,[11] Thomas Becker, MD,[12] Wolf O. Bechstein, MD,[2] Andreas Pascher, MD,[13] Richard Viebahn, MD,[3] Edward K. Geissler, PhD,[1] Hans J. Schlitt, MD,[1] and Stefan A. Farkas, MD[1]

**Background.** Pancreas transplantation is the only curative treatment option for patients with juvenile diabetes. Organ shortage and restrictive allocation criteria are the main reasons for increasing waitlists, leading to severe morbidity and mortality. We designed a study to increase the donor pool with extended donor criteria (EDC) organs (donor age, 50-60 years; body mass index, 30-34 kg/m$^2$). **Methods.** Utilization of EDC organs required the implementation of a new allocation system within Eurotransplant. The study was a prospective, multicenter, 2-armed trial. The primary endpoint was pancreas function after 3 months. Rejection episodes, kidney function, and waitlist time were secondary endpoints. Patients receiving an EDC organ were study group patients; recipients of standard organs were control group patients. Follow-up was 1 year. **Results.** Seventy-nine patients were included in 12 German centers, 18 received EDC organs and 61 received standard organs. Recipient demographics were similar. Mean EDC donor age was 51.4 ± 5 years versus 31.7 ± 12 in the control group. Insulin-free graft survival was 83.3% for EDC and 67.2% for standard organs ($P$ = 0.245) after 3 months. One-year pancreas survival was 83.3% and 83.5% in the EDC versus standard group. One-year kidney allograft survival was approximately 94% in both groups. Rejection episodes and morbidity were similar. **Conclusions.** The Extended Pancreas Donor Program (EXPAND) shows in a prospective trial that selected EDC organs of donors older than 50 years can be used with outcomes similar to standard-criteria organs, therefore showing potential to reduce organ shortage and waiting times. This study substantiates the full implementation of EDC organs in a pancreas allocation system.

(*Transplantation* 2018;102: 1330–1337)

*Received 20 August 2017. Revision received 15 December 2017.*

*Accepted 30 December 2017.*

*1 Department of Surgery, University Hospital Regensburg, Regensburg, Germany.*

*2 Department of General and Visceral Surgery, Goethe-University Hospital and Clinics, Frankfurt am Main, Germany.*

*3 Department of Surgery, University Hospital Knappschaftskrankenhaus Bochum, Ruhr-University Bochum, Bochum, Germany.*

*4 Department of General, Visceral and Vascular Surgery, University Hospital Jena, Jena, Germany.*

*5 Department of Surgery, University Hospital Grosshadern, Ludwig Maximilian's University, Munich, Germany.*

*6 Department of Surgery, University Hospital Bonn, Bonn, Germany.*

*7 Department of General, Visceral and Transplant Surgery, University Hospital Tübingen, Tübingen, Germany.*

*8 Department of General, Visceral and Transplantation Surgery, Johannes Gutenberg University Mainz, Mainz, Germany.*

*9 Department of Abdominal, Vascular, and Transplant Surgery, Cologne-Merheim Medical Center, Witten/Herdecke University, Köln, Germany.*

*10 Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany.*

*11 Department of General, Visceral and Transplant Surgery, University Hospital of Heidelberg, Heidelberg, Germany.*

*12 Department of General and Thoracic Surgery, University Hospital Schleswig-Holstein, Kiel, Germany.*

*13 Department of General, Visceral and Transplantation Surgery, Charité-University Medicine Berlin, Berlin, Germany.*

*Current address for S.A.F.: Klinik für Allgemein- und Viszeralchirurgie, St. Josefs Hospital Wiesbaden, Beethovenstrasse 20, 65189 Wiesbaden, Germany.*

*Current address for P.S.: Division of Transplant Surgery, Department of Surgery, Medical University of Graz, Auenbruggerplatz 29, 8036 Graz, Austria.*

*Current address for A.P.: Department für Chirurgie, Klinik für Allgemein- und Viszeralchirurgie, Universitätsklinikum Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany.*

*Trial registration: Trial registered at http://www.clinicaltrials.gov: NCT01384006.*

*The study was sponsored by the University Hospital Regensburg and was supported by research grants from Astellas and Novartis.*

*A.P.'s institution (University Hospital Regensburg) received a research grant from Astellas and Novartis to support the conduct of the trial. H.J.S. has received lecture honoraria and reimbursement of travel expenses from Novartis, Astellas, Pfizer, and Roche, and also receives research support from Pfizer and Novartis. S.A.F. has received lecture honoraria, reimbursement of travel expenses, and receives research support from Novartis, Astellas, BMS, and Roche. F.R. received travel grants and speaker's bureau from Novartis, Roche, Biotest, and Astellas.*

*All other authors declare no conflicts of interest.*

*A.P. and S.A.F. initiated, designed, and coordinated the study. A.P. collected and interpreted data for analysis, managed medical monitoring, and wrote the first article draft. E.K.G. and R.V. were involved in designing the study and critical data interpretation and analysis. A.A.S. was involved in launching and designing the study, as well as data collection and inclusion of study patients. R.V., P.S., A. W., H.A., S.M., S.N., M.H., M.A.S., B.B., P.S., T.B., W.O.B., A.P., F.R., and H.J.S. were involved in data collection and inclusion of study patients, local ethics approval, and critical intellectual discussion of the manuscript. All authors reviewed and approved the article.*

*Correspondence: Andrea Proneth, Department of Surgery, University Hospital Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany. (andrea.proneth@uniklinik-freiburg.de).*



*ISSN: 0041-1337/18/10208-1330*

*DOI: 10.1097/TP.0000000000002122*

Patients with type 1 (juvenile) diabetes mellitus experience long-term complications, mostly related to vascular disease. Associated nephropathy can lead to dialysis with its own major risk factors for cardiovascular disease and poor life quality. Simultaneous pancreas kidney (SPK) transplantation or pancreas transplantation after kidney (PAK) are the only curative treatment options for patients with type 1 diabetes and impaired kidney function.[1,2] Patients on the waitlist have only a 58% 4-year survival rate compared with 90% after SPK.[3] With this clear potential to restore life quality and length,[4-6] it is crucial to perform transplantation in these patients as soon as possible.

Unfortunately, waitlists are continually increasing, leading to overall progressive patient deterioration. In 2000, there were 195 people on the waitlist for pancreas transplantation in the Eurotransplant (ET) region, with a total of 301 transplantations performed; in 2015, the waitlist increased to 412 patients, but only 192 transplantations were performed. Therefore, waitlist times nearly doubled within 15 years and are now close to 2 years (ET data), predictably worsening outcomes and morbidity for these patients. When researching the reasons, we found that—with constantly increasing mean donor age—large numbers of pancreas allografts potentially available for transplantation were being excluded due to strict ET Pancreas Allocation System criteria. These criteria excluded donors older than 50 years and those with a body mass index (BMI) greater than 30 kg/m$^2$ (ET manual version, May 26, 2009). Because the average age of a postmortal organ donor in the ET area is 58 years, and almost 50% of German donors are older than 55 years, donor selection by age is a major donor organ shortage factor. Compounding the problem in Germany, "non–heart-beating" donors are not legally allowed. Thus, extension of the donor pool is only possible by using organs from donors with higher age or BMI.

Currently available retrospective data from centers outside the ET area suggest a similar outcome after transplantation using extended donor criteria (EDC) organs,[7,8] but no prospective-controlled trials have tested this presumption. Therefore, the aim of our multicenter trial was to investigate the hypothesis that organs from donors aged 50 to 60 years or with a BMI greater than 30 kg/m$^2$, using local allocation with shorter ischemic times, can be transplanted with similar results when compared with the standard criteria organs. This trial was performed at multiple clinical sites in Germany over a 4-year period.

## MATERIALS AND METHODS

### Study Design

The Extended Pancreas Donor Program (EXPAND) was conducted as a prospective, multicenter, single-blinded, nonrandomized, 2-armed trial comparing outcomes after SPK, pancreas transplantation alone (PTA), or PAK transplantation of organs with standard donor criteria to extended criteria donors. Extended criteria donors were defined as having a BMI of 30 to 34 kg/m$^2$ or between ages 50 and 60 years. Randomization was not possible because group assignment depended on the type of organ a patient was allotted by the ET allocation system. Patients who received a standard criteria organ were included in the control group, and patients receiving an EDC organ were included into the study group. Patients were blinded to the type of organ they received. The enrollment phase was 3 years with a 1-year follow-up period; the first patient was included in July 2011. The last patient visit was conducted in April 2015.

The primary endpoint was insulin-free graft survival (graft in situ with detectable c-peptide and no requirement of insulin application to the recipient) of the EDC pancreas allograft at 3 months posttransplantation. Insulin weaning policies were center-specific during the first month after transplantation. Overall survival (OS), pancreas graft survival (graft in situ with detectable c-peptide), kidney graft survival, as well as morbidity, and hospitalization data were assessed as secondary endpoints. Secondary endpoints additionally included biopsy-proven acute rejections and time on the waitlist. All patients on the waitlist for primary SPK, PTA, or PAK were trial eligible with inclusion criteria including being 18 years or older and a negative crossmatch. The main exclusion criteria were malignant diseases within the past 5 years before transplantation (excluding squamous cell carcinoma and basal cell carcinoma of the skin), as well as patients listed for pancreas retransplantation and women of childbearing potential not willing to take contraceptives.

Patients received a standardized immunosuppressive treatment consisting of induction therapy (depleting or nondepleting antibodies), steroids, tacrolimus, and mycophenolic acid/mycophenolate mofetil. Early withdrawal of steroid-specific immunosuppression use.

### Allocation

The allocation algorithm for potential deceased pancreas donors is regulated and defined in the ET handbook, *Pancreas Allocation Algorithms*. Before the EXPAND Study, the cutoff criteria for standard criteria donors were set to an age younger than 50 years or a BMI less than 30 kg/m$^2$. For these criteria, allocation is performed according to HLA matching to the recipient, urgency status of recipient, waitlist time, and so on. Local distribution aspects are not incorporated into the allocation system, often resulting in relatively long cold ischemic times. With the EXPAND study initiation, changes in the allocation of EDC organs in Germany in this distribution system were made (age, 50-60 years or BMI, 30-34 kg/m$^2$) as described in our study protocol.[9]

All deceased potential pancreas donors were screened for eligibility using the revised allocation algorithm. Organs meeting the standard criteria were allocated according to the previously existing system. Donors with extended criteria who were between 50 and 60 years of age or with a BMI of 30 to 34 kg/m$^2$ were allocated according to the newly implemented ET rescue allocation algorithm. These organs were allocated only regionally to ensure a recommended cold ischemia time (CIT) of less than 12 hours. The risk/benefit assessment of accepting the allocated organs due to criteria, such as serum amylase or lipase, donor time in the intensive care unit (ICU), reanimation procedures, or use of vasoactive drugs, were made at the discretion of the transplant surgeons in both groups, with no distinct cutoff lines.

### Study Oversight

The EXPAND study was an investigator-initiated trial for which the University Hospital Regensburg was the sponsor (trial registered at http://www.clinicaltrials.gov: NCT01384006). Funding was provided by grants from Astellas (Munich, Germany) and Novartis GmbH (Nürnberg, Germany); neither

company was involved in the trial design, analysis, or interpretation of the data. For accuracy, the sponsor monitored all primary and secondary endpoint data on site by verifying source data and case report form entries.

### Statistical Plan and Analysis

The sample size was calculated by means of the primary endpoint (ie, extended pancreas allograft survival rate after 3 months, assuming an expected rate of 80%[10,11]), whereas the minimal accepted survival rate was set to 60%. The 60% limit is based on the maximally acceptable lower-organ survival rate, as agreed upon during an EXPAND investigators meeting. The significance level of alpha (1-sided) was set to 0.05 and beta was set to 0.20, this is in accordance with the estimation of a 1-sided 90% confidence interval (CI) for the survival rate after 3 months. A sample size of 34 patients with an extended donor pancreas allograft achieves 80% power to distinguish between the 2 proportions, 60% (p0) and 80% (p1), using a 1-sided, binomial hypothesis test with a target significance level of 0.05. Assuming a maximal dropout rate of 5%, 36 patients would be required for the primary endpoint. The control group was planned to be at least equal in size, consisting of patients with a standard donor pancreas allograft for analyzing the secondary endpoints. The sample size calculation was performed using NCSS-PASS 2000. Sample size was estimated based on exact binomial probabilities. No power analysis for secondary endpoints was done.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary NC). Data are presented as mean ± SD for continuous variables and as an absolute number (%) for categorical data. Baseline characteristics were compared using Student *t* test and Fischer exact test due to the small sample size in the EDC group.

### Primary Endpoint

A 1-sided, exact binomial hypothesis test with a target significance level $\alpha = 0.05$ and a target power $1 - \beta = 0.80$ was used for analysis of the primary endpoint. The primary analysis was based on the ITT analysis set. However, a sensitivity analysis was performed on the per-protocol analysis set to assess the robustness of the results.

### Secondary Endpoints

OS was calculated from the date of transplantation to the date of death due to any cause. Surviving patients, or patients lost to follow-up, were classified as censored cases on the latest date they were confirmed to be alive. Overall organ allograft survival was calculated from the date of transplantation to the date of last contact when a patient finished the trial; all patients who died during the trial were considered as an event regarding organ survival. Organ allografts that survived until study end or organs of patients lost to follow-up were classified as censored cases on the latest date a patient was confirmed to be alive.

Differences in time-to-event data between the EDC and the standard organ group were analyzed using the method of Kaplan-Meier and the log-rank tests. Survival rates at 3 and 12 months were estimated according to the Kaplan-Meier product-limit survival estimates. Because of the small sample size in the EDC group, no multivariable Cox regression models were calculated.

Time in hospital and number of adverse events (AEs) were compared using the nonparametric Wilcoxon-Mann-Whitney *U* test. Proportions were compared using Fishers exact test. All secondary endpoints were analyzed in a purely exploratory manner.

## RESULTS

### Patient Recruitment

A total of 79 patients were included from 12 German centers in the control and EDC groups. The control group was completed in March 2013, with only inclusion of patients receiving an EDC organ allowed thereafter. However, Germany experienced a sharp reduction in total organ donor numbers during this period, requiring a recalculation of the sample size. As such, only 18 patients were included in the EDC group until the end of the inclusion period in December 2014. Although there were no premature patient withdrawals in the EDC group, the control group recorded 3 (4%) patients withdrawing their consent, 6 (9%) patients lost to follow-up, and 2 (3%) patient deaths (Figure 1). In the EDC group, inclusion was related to donor age of 50 years or older in most cases (17 cases, 94%; age range, 50-58 years), with only 1 organ allocated as EDC due to BMI greater than 30 kg/m$^2$ (1 case [6%]; BMI, 33; age, 35 years). One patient in each group received PTA, whereas all other patients received SPK.

### Recipient and Donor Characteristics

A summary of recipient demographic data is given in Table 1. There were no statistically significant differences between both groups. Notably, the following trends were noted in the EDC group when compared with the standard group: patients were older (47.7 years vs 43.7 years), suffered longer from diabetes (32.3 years vs 28.3 years) and required dialysis for a slightly longer period (3.2 years vs 2.8 years). Time on the waitlist was slightly shorter for EDC group patients (18.7 months vs 20.5 months). Almost all patients (87%) received the recommended immunosuppressive treatment consisting of tacrolimus, mycophenolic acid/mycophenolate mofetil, and steroids. In total, 4 patients in the EDC group and 6 patients in the standard group were switched to either cyclosporine or everolimus (1 in each group) during the study.

Donor demographics are presented in Table 2. Per definition, EDC donors were substantially older (51.4 years) than standard group donors (31.7 years). Notably, there was no difference in BMI between the EDC and the standard groups (23.3 kg/m$^2$ vs 24.0 kg/m$^2$, respectively) because only 1 donor was allocated as an extended organ for having a BMI greater than 30 kg/m$^2$. More female donors were found in the EDC group when compared with the standard group (78% vs 48%, respectively); no gender-specific outcome was detected in a subgroup analysis. The main cause of death for EDC donors was cerebral hemorrhage (89% vs 41% in the standard group), but none of the EDC donors died from traumatic injury (0% vs 34% in the standard group). There tended to be a higher prevalence of hypertension in EDC donors (28% vs 12% in the standard group). No substantial difference was observed in the duration of ICU stay (4.2 days vs 6.9 days), requirement of catecholamine treatment (72% vs 84%), or CIT (9.0 hours vs 10.2 hours) in the EDC group versus the standard group, respectively. More donors in the EDC group required insulin before procurement, when compared with the standard group (44% vs 20%, respectively).

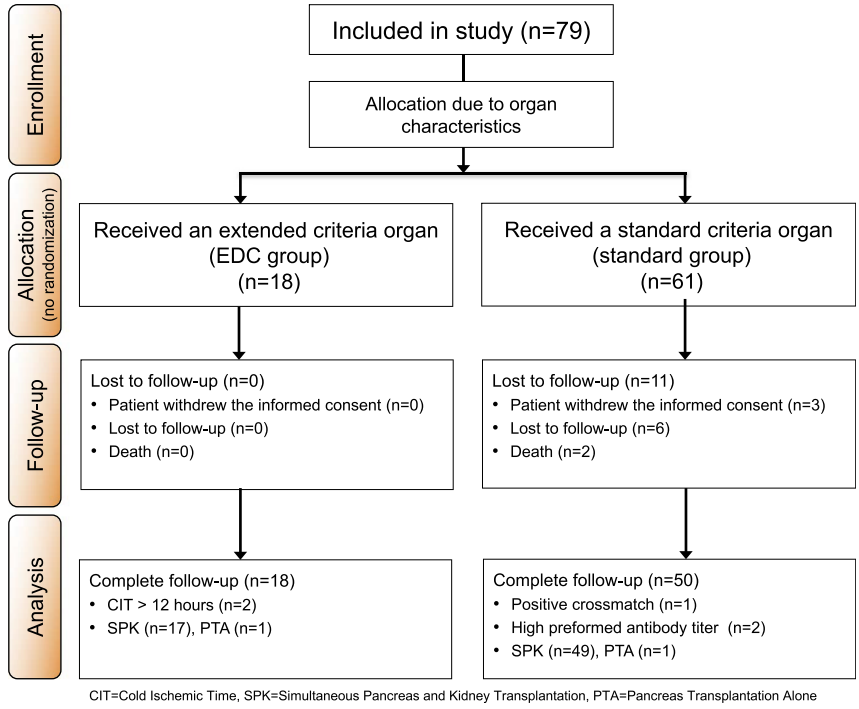


**FIGURE 1.** Patient disposition.

## Insulin-Free Graft Survival at 3 Months

The primary endpoint was analyzed as a combined endpoint of graft survival and function at 3 months, defined as insulin-free graft survival for the EDC group (graft in situ with detectable c-peptide and no requirement of insulin application to the recipient). The primary endpoint was met in 83% of the patients receiving EDC organs (90% CI, 0.62-0.95). Thus, the minimal accepted organ survival rate of 60% was not within the CI and reached statistical significance ($P$ = 0.043). Insulin-free graft survival at 3 months in the standard group was analyzed to compare outcome data. The standard organs showed an insulin-free graft survival rate of 67% at 3 months (90% CI, 0.56-0.77) ($P$ = 0.154). Graft survival comparison between both groups showed no significance ($P$ = 0.245) (Figure 2). Notably, 2 patients in the EDC group had a longer CIT than the advocated 12 hours (12.5 and 13.3 hours, respectively); 1 patient in the standard group showed a positive crossmatch, and 2 patients in the standard group were sensitized with a high antibody titer greater than 60%. After exclusion of these patients from the analysis (per-protocol analysis), both groups achieved an insulin-free graft survival of 81% at 3 months.

## Secondary Outcome Measures

Pancreas graft survival (detectable c-peptide, recipients might require insulin treatment) and kidney allograft survival, as well as overall patient survival throughout the follow-up period of 1 year, were analyzed as secondary endpoints and presented as Kaplan-Meier curves in Figure 3A-C. Organ loss of the transplanted pancreas occurred in 3 patients in the EDC group and in 10 patients in the standard group. This accounts to a probability of pancreas survival of 100% and 83.3% after 3 and 12 months in the EDC group versus 94.8% and 83.5% in the standard group, respectively. Reasons for pancreatectomy included pancreatitis (n = 5), primary nonfunction (n = 1), thrombosis (n = 3), partial resection due to thrombosis at month 12 (n = 1), hyperacute rejection (n = 1), and patient deaths (n = 2 in standard group). The probability of kidney survival was 100% and 94.4% in the EDC group after 3 and 12 months versus 94.8% and 94.4% in the standard group, respectively. Notably, 1 patient in the standard group underwent pancreas retransplantation and 1 in the EDC underwent kidney retransplantation.

**TABLE 1.**

**Recipient demographics**

| | EDC group (n = 18) | Standard group (n = 61) | *P* |
|---|---|---|---|
| Male/female | 12 (67)/6 (33) | 41 (67)/20 (33) | 0.965 |
| Age, y | 47.7 ± 8 | 43.7 ± 9 | 0.085 |
| Body weight, kg | 76.9 ± 15 | 73.5 ± 12 | 0.316 |
| Time of diabetes, y | 32.3 ± 9 | 28.3 ± 9 | 0.103 |
| Daily dose of insulin, IU | 33 ± 21 | 33 ± 19 | 0.940 |
| Medical history | | | |
| Nephropathy | 17 (94) | 61 (100) | 0.228 |
| Retinopathy | 14 (78) | 47 (77) | 1.000 |
| Neuropathy | 12 (67) | 34 (56) | 0.587 |
| Coronary heart disease | 5 (28) | 15 (25) | 0.766 |
| Peripheral arterial disease | 2 (12) | 11 (18) | 0.722 |
| Chronic dialysis | 16 (89) | 55 (90) | 0.875 |
| Hemodialysis/CAPD | 13 (81)/3 (19) | 46 (84)/9 (16) | 1.000 |
| Time on dialysis, y | 3.2 ± 3 | 2.8 ± 2 | 0.555 |
| Waiting time for transplantation, mo | 18.7 ± 13 | 20.5 ± 16 | 0.895 |

Data presented as mean ± SD or absolute number (%).
CAPD, continuous ambulatory peritoneal dialysis.

**TABLE 2.**

**Donor demographics**

| | EDC group (n = 18) | Standard group (n = 61) | *P* |
|---|---|---|---|
| Male/female | 4 (22)/14 (78) | 32 (52)/29 (48) | 0.031 |
| Age, y | 51.4 ± 5 | 31.7 ± 12 | <0.001 |
| BMI, kg/m$^2$ | 23.3 ± 4 | 24.0 ± 3 | 0.319 |
| Days in ICU | 4.2 ± 3 | 6.9 ± 12 | 0.358 |
| History of hypertension[a] | 5 (28) | 7 (12) | 0.059 |
| Requirement of vasoactive drugs | 13 (72) | 51 (84) | 0.313 |
| Requirement of insulin | 8 (44) | 12 (20) | 0.061 |
| Reason of death | | | |
| Trauma | 0 (0) | 21 (34.4) | 0.002 |
| Apoplexy | 1 (5.6) | 2 (3.3) | 0.545 |
| Cerebral hemorrhage | 16 (88.8) | 25 (41) | <0.001 |
| Other | 1 (5.6) | 13 (21.3) | 0.170 |
| CIT, h | 9.0 ± 3 | 10.2 ± 3 | 0.128 |

Data presented as mean ± SD or absolute number (%).
[a] History of hypertension was unknown for 29 (48%) of standard donors and 9 (50%) of extended donors.

There were no deaths in the EDC group compared with 2 deaths in the standard group due to multiorgan failure and sepsis. Both patients died in the early phase of the study, leading to an OS of 100% after 3 and 12 months in the EDC group and 96.6% in the standard group.

Assessment of transplanted pancreas function was achieved by measuring fasting blood glucose, hemoglobin $A_{1c}$, and C-peptide levels during follow-up visits (Figure 4A-C). Values in both groups were equally distributed, indicating a similar function in both groups. Serum creatinine was used to evaluate transplanted kidney function (Figure 4D), and no significant difference was noted.

### Safety analyses

Morbidity and mortality data are presented in Table 3. Patients transplanted with an EDC organ tended to have a longer median time in hospital after transplantation (36 days vs 26 days in the standard group). In-hospital morbidity did not differ between the groups. Classification of postoperative complications graded according to the Clavien-Dindo classification[12] revealed a higher need for intervention with general anesthesia (grade IIIb) in the EDC group (44% vs 20% in the standard group), whereas there were more life-threatening complications (10%) and 2 deaths in the standard group. Pancreatitis or bleeding/hematoma were the most common reasons for surgical reintervention. The number of AEs per patient was slightly higher in the EDC group (7.0 ± 2.68 vs 5.5 ± 2.47 in the standard group), whereas life-threatening AEs occurred exclusively in the standard group (11 events). Biopsy-proven rejection episodes occurred in 11% of the EDC patients and in 16% of the standard group patients.

## DISCUSSION

Results from this first prospective multicenter study evaluating the outcome of extended criteria pancreas transplantation indicate excellent outcomes, especially for older donors. In our trial, 1-year graft survival after pancreas transplantation using primarily donors older than 50 years achieved allograft survival of 83.3%, which was equal to the rates attained using standard criteria (83.5%) with the donor age averaging 31.7 years. Other groups have retrospectively looked at outcomes after pancreas transplantation using older donors and reported 1-year graft survival ranging from 69% to 81.2%[7,13,14]; notably, however, the donor age in these analyses was held to a "lower bar," where age limit did not exceed 45 years. The prospective conduct of our trial, combined with further extension of the age limit 20 years beyond standard donors, paves the way for transplanting more patients on the growing transplant waitlists. Key elements we incorporated for successful extension of donor limits included local organ procurement to minimize ischemia times and the option to assess organ quality by the local transplant team.

The preprocurement pancreas suitability score consists of different donor factors and was introduced in 2008 in the ET area for the assessment of pancreas organ quality,[15] with a critical cutoff score of 17. In our trial, the EDC group organs presented, in fact, with a higher (ie, worse) score than standard organs (17.5 ± 2 vs 16.0 ± 3, respectively). Although donor age is included in the preprocurement pancreas suitability score, there are several other factors also associated with a worse outcome, such as nontrauma death, high BMI, and long CIT. In EXPAND, EDC donors were 20 years older than the standard donors (51.4 years vs 31.7 years), but notably also died primarily from cerebrovascular insult. This is an interesting point because Axelrod et al.[16] showed that a cerebrovascular cause of death is a predictor of graft failure when implementing a donor risk index for pancreas transplantation. Other retrospective studies also found that "nontrauma" death[17] is associated with a higher rate of technical failure, along with a BMI greater than 30 kg/m$^2$ and CIT longer than 12 hours.[18] Although BMI and CIT were below these critical cutoff points in both groups in our trial, age and reason for death would clearly have predicted a worse outcome for the EDC organs. Furthermore,

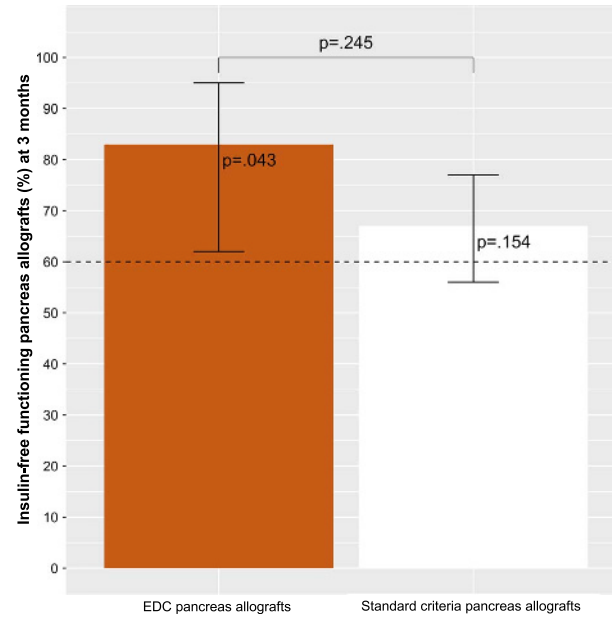


**FIGURE 2.** Insulin-free pancreas graft survival at 3 months (functioning pancreas allografts with detectable c-peptide and no requirement of insulin treatment to the recipient).

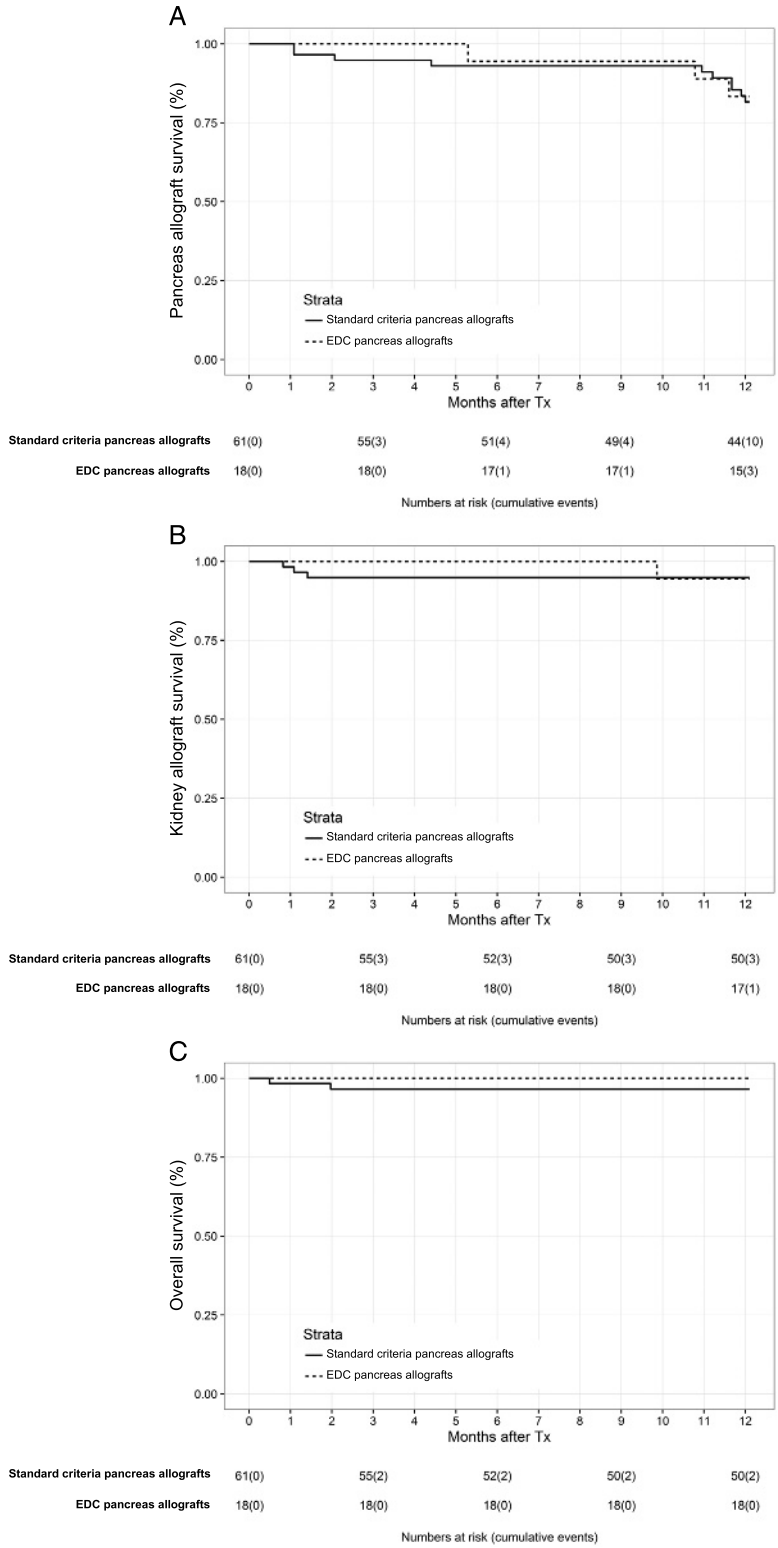


**FIGURE 3.** Survival data. A, Pancreas graft survival (viable pancreas allografts with detectable c-peptide, recipient might require insulin treatment). B, Kidney graft survival, C, OS.

adding to the expectation of poorer outcomes in the EDC group, EDC organs are generally transplanted to older recipients suffering longer from diabetes and having spent more time on dialysis. In our trial, recipients had been on dialysis for 3.2 (EDC) versus 2.8 (standard) years. Despite these higher risk factors, our study did not reveal disadvantages for EDC recipients. In fact, the standard group patients experienced 8 life-threatening events during the early posttransplant phase, but there were no such events in the EDC group. Mortality was higher in the standard group with 2 patient deaths and no deaths in the EDC group. Data revealed only a slightly longer hospitalization time for

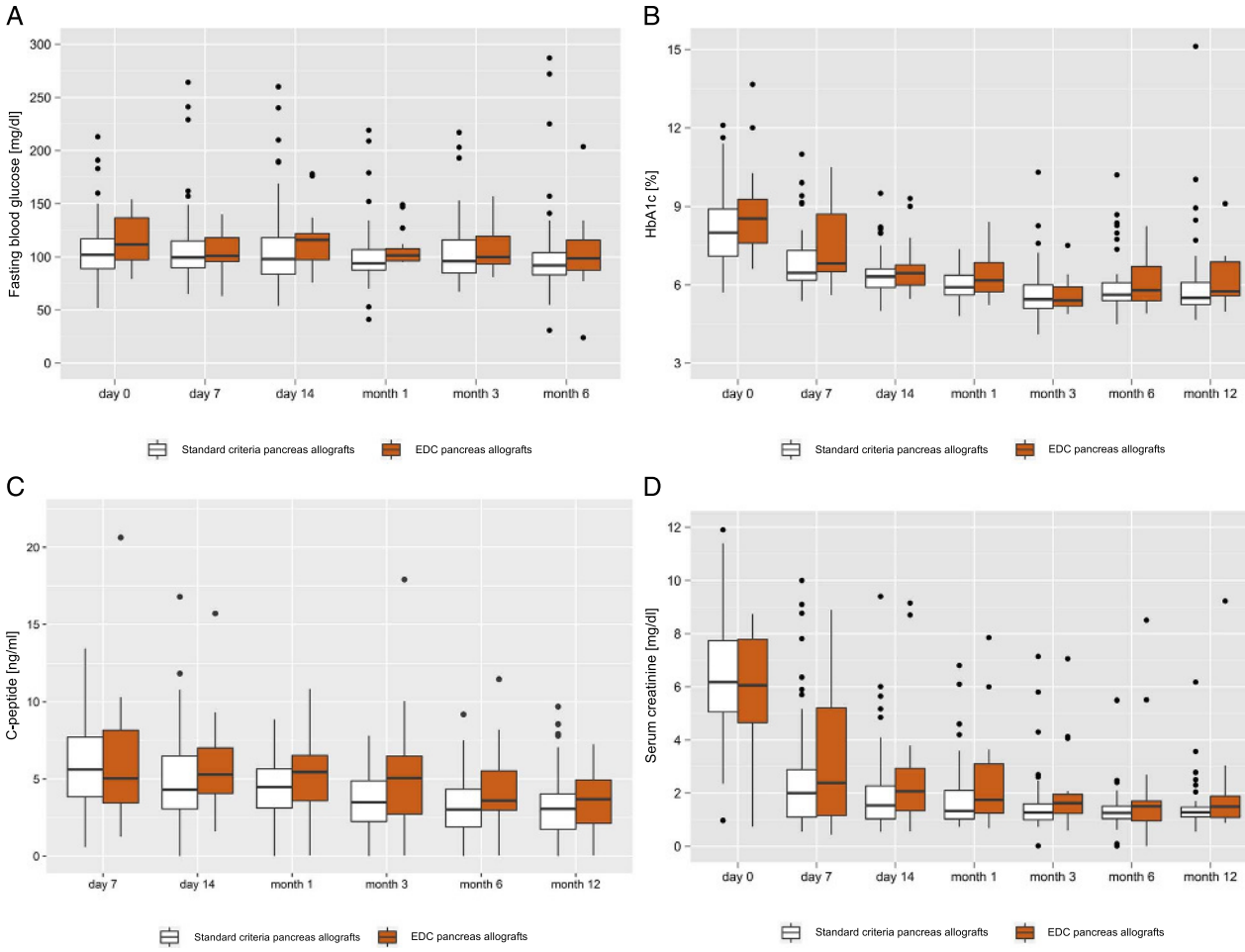


**FIGURE 4.** Organ function. A, Fasting blood glucose. B, $HbA_{1c}$. C, C-peptide. D, Serum creatinine. $HbA_{1c}$, hemoglobin $A_{1c}$.

EDC patients, and overall in-hospital morbidity showed also only a slight increase of AEs in EDC patients. We conclude that the EDC donor organs selected in our trial produced 1-year results in recipients that were as good as standard organ recipients.

Within EXPAND, acceptance of an organ in terms of a high BMI as an extended criterion was an option. Despite this option, only 1 organ from a donor with a BMI greater than 30 $kg/m^2$ was used as an EDC organ, resulting in no real difference in BMI values (23.3 vs 24.0) between the EDC and standard groups. Therefore, unfortunately, our study can only address the issue of using older donors and does not provide insight into whether donor BMI can be extended. In terms of accepting a marginal organ, BMI is crucial to most transplant surgeons for fear of a higher rate of pancreatitis and graft failure. Notably, organs from obese donors may be more successful for islet isolation[19] and probably should primarily be allocated for islet cell transplantation.[20,21] Whether they will be suitable for pancreas transplantation remains to be elucidated.

In the experience of our participating surgeons, and consistent with our results, their discretion regarding evaluation of the macroscopic organ quality appears to be a major factor. This general observation leads to the recommendation that an important factor contributing to good outcomes when using older organs is the selection of dedicated and experienced centers. Notably, transplantation of the EDC organs was only performed in 4 high-volume centers of the 12 participating centers. However, this means that a substantial portion of the standard group patients were transplanted in low-volume centers, leaving open the possibility of a slight bias toward inferior outcomes in the control group.[22]

Considering our outcome data, there is a clear potential impact for patients on the waitlist. In an analysis of the OPTN registries, Gruessner et al.[3] noted 5-year graft survival rates of 61% from donors older than 45 years, as compared with 72% from standard donors with a 5-year patient survival of 81% and 84.5%, respectively. Importantly, patients remaining on the waitlist only achieved a 5-year survival rate of 45%. This underscores the importance of early transplantation and the critical need for more organs to improve outcomes of otherwise long waitlisted patients. We managed to reduce the time on the waitlist from 20.5 to 18.7 months when patients were transplanted with an EDC organ. With further experience in the use of EDC organs, waiting times could be reduced even further. For sensitized patients or patients with blood group type complications, the typically longer waiting times could be reduced substantially by using older EDC organs, even if long-term organ function should prove to be shorter for older organs. Notably, long-term outcomes were not evaluated in our trial, so this aspect still needs to be tested in further studies.

**TABLE 3.**

**Morbidity and mortality data**

| | EDC group (n = 18) | Standard group (n = 61) | *P* |
|---|---|---|---|
| Time in hospital: median (IQR), d[a] | 36 (18-51) | 26 (19-37) | 0.409 (WMW) |
| Overall mortality | 0 (0) | 2 (3) | 0.433 (LR) |
| In-hospital morbidity | 13 (72) | 43 (70) | 1.00 (FT) |
| Classification Clavien-Dindo | | | |
| None | 5 (28) | 18 (30) | 0.644 (WMW)[b] |
| I | 1 (6) | 14 (23) | |
| II | 4 (22) | 7 (11) | |
| IIIa | 0 (0) | 2 (3) | |
| IIIb | 8 (44) | 12 (20) | |
| IVa | 0 (0) | 6 (10) | |
| IVb | 0 | 0 | |
| V | 0 (0) | 2 (3) | |
| No. AEs | 126 | 336 | |
| AE number per patient | 7.00 ± 2.68 | 5.51 ± 2.47 | 0.052 (WMW) |
| No. severe AE | 21 (17) | 40 (12) | 0.216 (FT) |
| No. life-threatening AE | 0 (0) | 11 (3) | <0.001 (FT) |
| Biopsy-proven acute rejection | 2 (11) | 10 (16) | 0.724 (FT) |

Data presented as median (IQR), mean ± SD, or absolute number (%).
[a] 2 (3%) patients died in hospital and 2 (3%) patients withdraw from study in the standard group.
[b] *P* value indicates if one of the ordinal distributions is stochastically greater than the other.
WMW, Wilcoxon-Mann-Whitney test; LR, log-rank test; FT, Fischer exact test.

## CONCLUSIONS

In conclusion, the EXPAND study is the first prospective multicenter trial comparing and evaluating the outcomes of standard criteria in deceased donor pancreas organs to extended criteria organs. Our results show excellent outcomes after transplantation with organs from donors older than 50 years, when a careful selection is made at the discretion of the transplant surgeon. This finding also strengthens the necessity for evaluation and harvesting of organs by the (local) transplantation teams with regional allocation. More importantly, EDC organs did not pose a higher risk for early graft loss or morbidity, and no overall contraindicative disadvantages were observed over the first year posttransplantation. This clinical trial substantiates the full implementation of older donors in the pancreas organ allocation process, leading to a potentially significant expansion of the available donor pool.

## ACKNOWLEDGMENTS

The authors would like to thank the responsible staff within ET and the Deutsche Stiftung Organtransplantation (DSO) for contribution to establishment of the rescue allocation system, with special thanks to Axel O. Rahmel and Undine Samuel as without their cooperation the study would not have been possible. The authors would also like to thank the supportive personnel at each site, especially the study nurses for patient monitoring and supportive contributions. We greatly appreciate the devoted efforts of our study statistician, Florian Zeman. The authors are also very grateful for the input of the clinical trials group in the Department of Surgery, University Hospital Regensburg. In particular, the authors want to express their gratitude to Dr. Johanna Forster and Ines Holub (on-site monitoring), Christine Ross-Cavanna (administrative assistance), Kristin Geissler (database management), and Susanne Melter (patient monitoring).

## REFERENCES

1. Sollinger HW, Odorico JS, Becker YT, et al. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. *Ann Surg*. 2009;250:618–630.
2. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. *Lancet*. 2009;373:1808–1817.
3. Gruessner RW, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. *Am J Transplant*. 2004;4:2018–2026.
4. Becker BN, Brazy PC, Becker YT, et al. Simultaneous pancreas-kidney transplantation reduces excess mortality in type 1 diabetic patients with end-stage renal disease. *Kidney Int*. 2000;57:2129–2135.
5. Ojo AO, Meier-Kriesche HU, Hanson JA, et al. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. *Transplantation*. 2001;71:82–90.
6. Tyden G, Bolinder J, Solders G, et al. Improved survival in patients with insulin-dependent diabetes mellitus and end-stage diabetic nephropathy 10 years after combined pancreas and kidney transplantation. *Transplantation*. 1999;67:645–648.
7. Salvalaggio PR, Schnitzler MA, Abbott KC, et al. Patient and graft survival implications of simultaneous pancreas kidney transplantation from old donors. *Am J Transplant*. 2007;7:1561–1571.
8. Andreoni KA, Brayman KL, Guidinger MK, et al. Kidney and pancreas transplantation in the United States, 1996-2005. *Am J Transplant*. 2007; 7(5 Pt 2):1359–1375.
9. Proneth A, Schnitzbauer AA, Zeman F, et al. Extended pancreas donor program—the EXPAND study rationale and study protocol. *Transplant Res*. 2013;2:12.
10. Boggi U, Mosca F, Vistoli F, et al. Ninety-five percent insulin independence rate 3 years after pancreas transplantation alone with portal-enteric drainage. *Transplant Proc*. 2005;37:1274–1277.
11. Krieger NR, Odorico JS, Heisey DM, et al. Underutilization of pancreas donors. *Transplantation*. 2003;75:1271–1276.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
13. Boggi U, Del Chiaro M, Signori S, et al. Pancreas transplants from donors aged 45 years or older. *Transplant Proc*. 2005;37:1265–1267.
14. Schenker P, Wunsch A, Ertas N, et al. Long-term results after simultaneous pancreas-kidney transplantation using donors aged 45 years or older. *Transplant Proc*. 2008;40:923–926.
15. Vinkers MT, Rahmel AO, Slot MC, et al. How to recognize a suitable pancreas donor: a Eurotransplant study of preprocurement factors. *Transplant Proc*. 2008;40:1275–1278.
16. Axelrod DA, Sung RS, Meyer KH, et al. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. *Am J Transplant*. 2010;10:837–845.
17. Humar A, Ramcharan T, Kandaswamy R, et al. Technical failures after pancreas transplants: why grafts fail and the risk factors—a multivariate analysis. *Transplantation*. 2004;78:1188–1192.
18. Vrakas G, Arantes RM, Gerlach U, et al. Solitary pancreas transplantation: a review of the UK experience over a period of 10 yr. *Clin Transplant*. 2015; 29:1195–1202.
19. Matsumoto I, Sawada T, Nakano M, et al. Improvement in islet yield from obese donors for human islet transplants. *Transplantation*. 2004;78: 880–885.
20. Neidlinger NA, Odorico JS, Sollinger HW, et al. Can 'extreme' pancreas donors expand the donor pool? *Curr Opin Organ Transplant*. 2008;13: 67–71.
21. Hudson A, Bradbury L, Johnson R, et al. The UK pancreas allocation scheme for whole organ and islet transplantation. *Am J Transplant*. 2015;15:2443–2455.
22. Kopp W, van Meel M, Putter H, et al. Center volume is associated with outcome after pancreas transplantation within the Eurotransplant region. *Transplantation*. 2017;101:1247–1253.