Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial

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Summary

Background Islet transplantation is indicated for patients with type 1 diabetes with severe hypoglycaemia or after kidney transplantation. We did a randomised trial to assess the efficacy and safety of islet transplantation compared with insulin therapy in these patients.

Methods In this multicentre, open-label, randomised controlled trial, we randomly assigned (1:1) patients with type 1 diabetes at 15 university hospitals to receive immediate islet transplantation or intensive insulin therapy (followed by delayed islet transplantation). Eligible patients were aged 18–65 years and had severe hypoglycaemia or hypoglycaemia unawareness, or kidney grafts with poor glycaemic control. We used computer-generated randomisation, stratified by centre and type of patient. Islet recipients were scheduled to receive 11 000 islet equivalents per kg bodyweight in one to three infusions. The primary outcome was proportion of patients with a modified β-score (in which an overall score of 0 was not allocated when stimulated C-peptide was negative) of 6 or higher at 6 months after first islet infusion in the immediate transplantation group or 6 months after randomisation in the insulin group. The primary analysis included all patients who received the allocated intervention; safety was assessed in all patients who received islet infusions. This trial is registered with ClinicalTrials.gov, number NCT01148680, and is completed.

Findings Between July 8, 2010, and July 29, 2013, 50 patients were randomly assigned to immediate islet transplantation (n=26) or insulin treatment (n=24), of whom three (one in the immediate islet transplantation group and two in the insulin therapy group) did not receive the allocated intervention. Median follow-up was 184 days (IQR 181–186) in the immediate transplantation group and 185 days (172–201) in the insulin therapy group. At 6 months, 16 (64% [95% CI 43–82]) of 25 patients in the immediate islet transplantation group had a modified β-score of 6 or higher versus none (0% [0–15]) of the 22 patients in the insulin group (p<0·0001). At 12 months after first infusion, bleeding complications had occurred in four (7% [2–18]) of 55 infusions, and a decrease in median glomerular filtration rate from 90·5 mL/min (IQR 76·6–94·0) to 71·8 mL/min (59·0–89·0) was observed in islet recipients who had not previously received a kidney graft and from 63·0 mL/min (55·0–71·0) to 57·0 mL/min (45·5–65·1) in islet recipients who had previously received a kidney graft.

Interpretation For the indications assessed in this study, islet transplantation effectively improves metabolic outcomes. Although studies with longer-term follow-up are needed, islet transplantation seems to be a valid option for patients with severe, unstable type 1 diabetes who are not responding to intensive medical treatments. However, immunosuppression can affect kidney function, necessitating careful selection of patients.

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Introduction

Islet transplantation provides clinical benefits for patients with type 1 diabetes experiencing hypoglycaemia unawareness and severe glycaemic variability.[1–4] According to several non-controlled or small, non-randomised, controlled studies, islet transplantation improves quality of life[5] and metabolic control,[2–4,6,7] and prevents severe hypoglycaemia[8] and progression of microangiopathy.[9,10] Islet transplantation, done after kidney transplantation in patients with type 1 diabetes and end-stage renal disease improves kidney graft function and survival.[11] However, no prospective, randomised trial has been done to assess the efficacy of islet transplantation.

We aimed to compare, in a randomised controlled trial, the efficacy of allogeneic islet transplantation with that of insulin therapy for improving metabolic

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Research in context

Evidence before this study

We searched PubMed from Jan 1, 2000, to Dec 31, 2008, using the search terms "islet transplantation" AND "trial", with the clinical trial filter activated to identify clinical trials of islet transplantation in type 1 diabetes reported in English only. We excluded reports of islet xenotransplantation, auto-transplantation, islet transplantation in type 2 diabetes, pancreas transplantation, and combined stem-cell transplantation. We also reviewed the five annual reports of the Collaborative Islet Transplant Registry (published between 2004 and 2008). We identified ten clinical trial reports, originating from North America (n=8), Asia (n=1), and Europe (n=1). Most of these trials were phase 2 studies, and none were randomised controlled trials. Outcomes were not consistently reported because the objectives of transplantation had not been consensually defined in 2008 when the TRIMECO trial was designed. The most common outcomes reported were insulin independence and C-peptide secretion. As of 2008, 50–79% of recipients were insulin independent at 1 year after islet transplantation and C-peptide secretion was restored in 90% of recipients. These results led some countries to provide insurance coverage for this procedure, but several governmental agencies requested additional, controlled studies, leading to the design of the TRIMECO trial. Since our study was initiated, in 2012, the Collaborative Islet Transplant Registry reported an insulin independence rate of 44% at 3 years after transplantation. In 2016, findings from a multicentre, single-arm, phase 3 study in North America showed that 42 (88%) of 48 patients achieved an HbA_{1c} of less than 7% without severe hypoglycaemic events at 1 year after transplantation.

Added value of this study

To our knowledge, this study is the first randomised controlled trial in the field of islet transplantation. We showed that, compared with insulin therapy, at 6 months, islet transplantation was effective at achieving optimal glycaemic control in patients with unstable type 1 diabetes or in patients with type 1 diabetes after kidney transplantation. Furthermore, compared with baseline, the effect of transplantation was maintained at 12 months. We found that the main risks of islet transplantation are bleeding complications and adverse events associated with immunosuppression.

Implications of all the available evidence

Islet transplantation improves metabolic outcomes in patients with unstable type 1 diabetes and in patients with type 1 diabetes who have received kidney grafts and have poor glycaemic control, and should be included in the stepped-care approach to treatment of these patients. Future studies will need to address the long-term effectiveness of islet transplantation, and further research is needed to establish the place of islet transplantation therapy versus new technologies, such as glucose-sensor-assisted therapy and automated insulin delivery.

outcomes in patients with type 1 diabetes who have severe hypoglycaemia or poorly controlled glycaemia after receipt of kidney grafts.

Methods

Study design and participants

TRIMECO was a phase 3, open-label, two-arm, multicentre, randomised controlled trial involving 15 university hospitals in France and three islet preparation units (two in France and one in Switzerland; appendix). TRIMECO was designed at the request of the French Health Authority as a prerequisite for evaluating coverage of islet transplantation by French health insurance.

Eligible patients were aged 18–65 years with type 1 diabetes diagnosed at least 5 years previously and had basal and stimulated C-peptide concentrations of less than 0·1 nmol/mL. To be eligible for islet transplantation, patients had to have severe glycaemic lability, associated with at least two severe hypoglycaemic events per year, severe impairment of quality of life related to hypoglycaemia, or hypoglycaemia unawareness (patient unaware of blood glucose concentrations <3 mmol/L [<54 mg/dL]). A severe hypoglycaemic event was defined as one in which the patient required third-party assistance for its correction. Patients with type 1 diabetes who had received a kidney graft were eligible for islet transplantation if they had a functional kidney graft (glomerular filtration rate >50 mL/min per 1·73 m², proteinuria <0·5 g per day, or both) and poor glycaemic control or substantial deterioration in quality of life related to diabetes. In all patients, appropriate attempts to reach optimal glycaemic control had been unsuccessful despite regular adjustment of insulin therapy and use of an educational approach (carbohydrate counting, flexible insulin therapy, increase of glycaemic goal) by multidisciplinary staff (diabetologists, dieticians, nurses, and psychologists). Exclusion criteria included an insulin requirement greater than 0·85 IU/kg per day, a BMI greater than 30 kg/m², and several other diseases or conditions; full exclusion criteria and non-permitted treatments are listed in the appendix. A committee composed of investigators from at least half of the study centres reviewed each patient's suitability for islet transplantation through monthly telephone conferences. A multidisciplinary independent committee validated the inclusion of selected patients.

This study was approved by the French Committee for the Protection of Persons Participating in Biomedical Research (approval number 09-CHUG-21), and clinical trial authorisation was obtained from the French National Competent Authority (2008-A01554-51). Written informed consent was obtained from all patients.

Randomisation and masking

Patients were randomly assigned (1:1) to immediate islet transplantation or to insulin therapy for 6 months followed by islet transplantation (insulin group) with a computer-generated randomisation stratified by centre and type of patient (islet transplantation alone *vs* islet transplantation after kidney graft). Randomisation was equilibrated per random-sized blocks of two to four patients. This trial was open label (not masked) for all participants, investigators, and the statistician.

Procedures

Patients assigned to immediate islet transplantation were immediately registered on the islet transplantation waiting list and transplanted as soon as a compatible preparation was available. Pancreases were obtained from brain-dead, multi-organ donors procured through the Swiss Transplant Agency and the French Biomedicine Agency. Donor criteria for pancreas acceptability and islet isolation, culture, and transplantation procedures have been previously described.[4] Patients were scheduled to receive 11 000 islet equivalents (IEQ) per kg bodyweight in one to three infusions, depending on the number of IEQ available per preparation. The immunosuppressive regimen consisted of mycophenolic acid and tacrolimus with thymoglobulin induction for the first islet infusion, basiliximab induction for the second and third infusions, and etanercept and pentoxifylline during the induction period. Details of the full immunosuppressive regimen, including drug doses and routes of administration, are in the appendix.

Patients assigned to the insulin group were treated with insulin for 6 months and registered on the islet transplantation waiting list at the end of this period. These patients were asked to do at least four capillary glucose tests per day, to practice carbohydrate counting after appropriate education, and to apply flexible insulin therapy. For patients treated with multiple daily injections, pump therapy was proposed and started if accepted by patients. Insulin doses were adjusted every 3 months by the investigator to achieve an HbA_{1c} of less than 7% (58 mmol/mol) without severe hypoglycaemia. Insulin pumps with low glucose thresholds or predictive suspend features were not available during most of the study period.

To assess islet transplantation outcomes at 12 months after their first infusion, patients assigned to both groups underwent clinical and metabolic evaluations (details in appendix). Criteria for removal of a patient from the study are described in the appendix.

Outcomes

The primary outcome was the proportion of patients with a modified β-score of 6 or higher 6 months after the first infusion in the immediate transplantation group and 6 months after randomisation in the insulin group. The classic β-score is a composite score that gives two points each for normal fasting glucose (≤5·5 mmol/L [100 mg/dL]), HbA_{1c} (≤6·1% [43·2 mmol/mol]), stimulated or basal C-peptide (≥0·3 nmol/L [1 ng/mL]), and absence of insulin or oral hypoglycaemic drug use. No point is given if fasting glucose is 7 mmol/L or higher, HbA_{1c} is 6·9% (51·9 mmol/mol) or higher, C-peptide secretion is undetectable on stimulation (<0·1 nmol/L [0·3 ng/mL]), or daily insulin use is 0·25 U/kg or higher, and one point is given for intermediate values. The overall score is 0 when stimulated C-peptide is negative. Thus, the classic β-score can range from 0 (no graft function) to 8 (optimal graft function); a β-score of 6 or higher is defined as graft success.[12] To analyse the effect of insulin treatment on metabolic outcomes in insulin-treated patients, we used a modified β-score in which the overall score was not 0 when stimulated C-peptide was negative. This modified β-score permited a composite metabolic evaluation in the insulin group, which would not have been possible with the classic β-score in which the C-peptide measurement overwhelms the score.

Key secondary outcomes were the individual outcomes of HbA_{1c}, C-peptide, insulin requirements, and fasting glycaemia; a composite outcome of an HbA_{1c} of less than 7% (58 mmol/mol) in the absence of severe hypoglycaemia; and health-related quality of life assessed with the 36-item Short Form Health Survey (SF-36) and the Diabetes Quality of Life questionnaire.[5] These outcomes were assessed 6 months after first infusion in the immediate transplantation group, 6 months after randomisation in the insulin therapy group, and 12 months after first infusion in the entire cohort. Other secondary outcomes were the mean amplitude of glycaemic excursions (MAGE)[13] and the Clarke score (hypoglycaemia awareness),[14] measured for the entire cohort at 12 months after first islet infusion (defined in the appendix). Because of a technical issue in the case report form, the MAGE index and Clarke score 6 months after islet infusion were not collected prospectively, thus these are not reported for the 6 month timepoint.

We set 7% (58 mmol/mol) as the cutoff value for HbA_{1c} according to American Diabetes Association (ADA) standards of medical care.[15] Insulin independence (defined as the ability to maintain HbA_{1c} <7% [58 mmol/mol], 2-h postprandial glucose <10 mmol/L without exogenous insulin, and with a fasting or stimulated plasma C-peptide ≥0·17 nmol/L) in the immediate transplantation group at 6 months and in the entire cohort at 12 months was also assessed as a predefined secondary outcome.

As a predefined secondary endpoint, we did a cost analysis in both groups according to the hospital perspective and for the 6 months of follow-up to establish the median cost per patient. Information about use of in-hospital resources was collected prospectively at each centre and for each patient. Medical costs in the immediate transplantation group were defined as those

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See **Online** for appendix

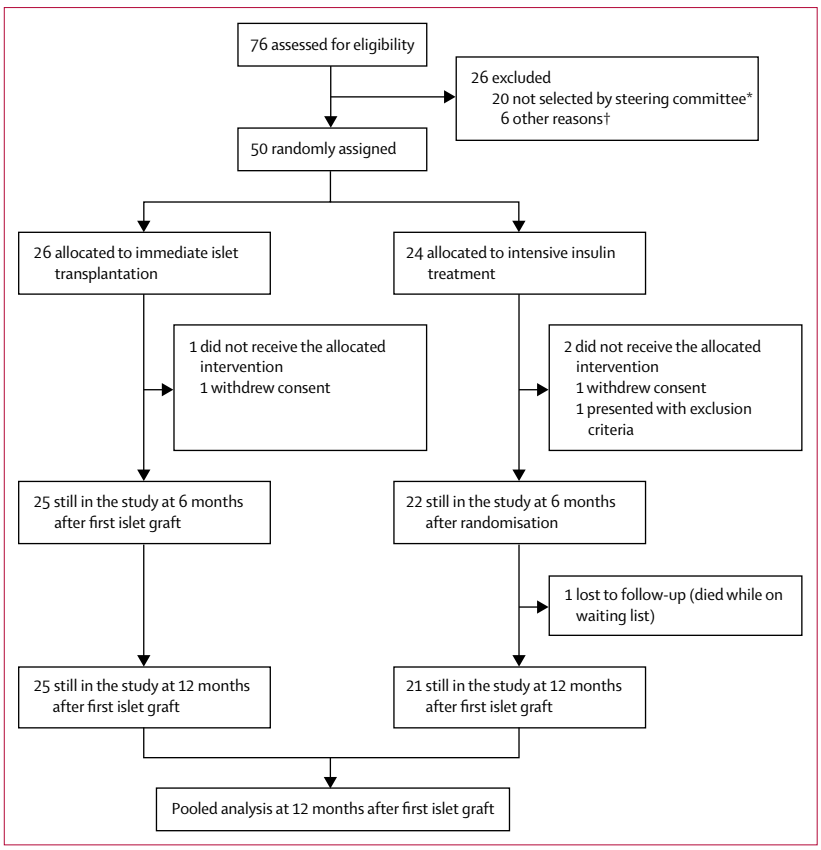


Figure 1: **Trial profile**
*These individuals developed exclusion criteria between eligibility assessment and selection. †Other reasons were required sample size had been achieved (n=4), withdrawal of consent (n=1), and self-reported severe ischaemic cardiopathy (n=1).

associated with pancreas procurement, islet isolation, hospital stay, induction therapy, and follow-up in hospital (ie, treatments, consultations, biology, radiology, nursing care). Medical costs in the insulin group were defined as those associated with follow-up in hospital. Unit costs were applied to the resource-use data and valued in 2014 euros.

We also did post-hoc analyses of glomerular filtration rate and β-2 score (defined in appendix) at 6 months (by group) and at 12 months (whole cohort).

We assessed serious adverse events (SAEs) reported between randomisation and 12 months after the first transplantation using the System Organ Class in the medical dictionary for regulatory activities.[16] An SAE was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires in-patient hospital admission or prolongation of existing hospital stay, or results in persistent or significant disability or incapacity or in a congenital anomaly or birth defect. An independent data and safety monitoring board composed of four experts was informed of all suspected, unexpected SAEs and was authorised to recommend suspension or early termination of the trial.

Statistical analysis

We estimated the required sample size on the basis of previous studies[17–19] showing that a modified β-score of 6 or higher was attained by 55% of patients who received immediate transplantation at 6 months after the first infusion and by 5% of patients who received insulin at 6 months after randomisation. Assuming a one-sided α value of 0·05 and no interaction (p>0·1) between the treatment group and patient type (patient with unstable diabetes *vs* kidney graft recipient), we calculated that enrolling 16 patients per group would give the study 95% power to detect a difference between the groups in the primary endpoint. We increased the sample size to 50 patients (25 per group) to account for withdrawals and to ensure identification of an appropriate recipient for each islet preparation and avoid islet waste. Sample size calculation was done with NQuery Advisor 7.0.

Statistical analysis was done with the usual procedures of data management and database locking using Stata version 13.1. The primary analysis included all patients who received the allocated intervention (excluding those who presented with exclusion criteria or withdrew their consent), and the result of this analysis was confirmed in the per-protocol population, which excluded one patient who received a total islet mass of less than 9000 IEQ per kg bodyweight. The definition of the per-protocol population was added to the statistical analysis plan before locking of the database, but was not approved by an amendment to the protocol. Safety was assessed in all patients who received islet infusions. Statistical analyses were done assuming a type I error of 0·05.

Categorical data are reported as numbers and percentages with 95% CIs. Continuous data are reported as medians with IQRs. For the between-group analysis at 6 months, we compared continuous variables using the Mann-Whitney *U* test and categorical variables using Fisher's exact test or the χ^2 test, as applicable. To compare change between baseline and 12 months after first injection for all patients who received islet transplantations, we used the paired Wilcoxon test for continuous variables and McNemar's test for categorical variables.

For one patient in the islet transplantation group, we used clinical and biological data collected at 11 months after first injection because data at 12 months' follow-up were missing. For two patients in the insulin group, we used clinical and biological data collected at 3 months' or 9 months' follow-up because data at 6 months' follow-up were missing. Follow-up was difficult in the patient for whom 9 months' follow-up data were used: the patient missed the visit at 6 months because of personal reasons and the visit was scheduled 3 months later. This patient did not receive a transplant before 9 months. We registered one patient in the insulin group on the islet transplantation waiting list earlier than planned in the protocol because of multiple and recurrent severe hypoglycaemia with coma, seizure,

	Immediate islet transplantation group (n=25)	Insulin group (n=22)	Total (n=47)
Type of patient (based on inclusion criteria)			
Severe glycaemic lability (with severe hypoglycaemia)	18 (72%)	18 (82%)	36 (77%)
Severe glycaemic lability (with hypoglycaemia unawareness)	2 (8%)	0	2 (4%)
Kidney graft recipients with poor glycaemic control	5 (20%)	4 (18%)	9 (19%)
Sex			
Male	13 (52%)	7 (32%)	20 (43%)
Female	12 (48%)	15 (68%)	27 (57%)
Age (years)	52 (40 to 57)	51 (42 to 58)	51 (41 to 58)
BMI (kg/m²)	22·9 (21·9 to 25·5)	23·9 (22·2 to 25·5)	23·7 (21·9 to 25·5)
Duration of diabetes (years)	34 (25 to 41)	30 (24 to 37)	30 (24 to 38)
HbA_{1c} (%)	8·1% (7·4 to 8·9)	8·1% (7·7 to 8·6)	8·1 (7·4 to 8·9)
HbA_{1c} (mmol/mol)	65 (57·4 to 73·8)	65·5 (60·7 to 70·3)	65·0 (57·4 to 73·8)
Fasting blood glucose (mmol/L)	8·1 (5·4 to 12·6)	9·8 (6·3 to 13·6)	9·1 (5·9 to 13·0)
Insulin requirements			
Units per day	36 (27 to 41)	30 (27 to 38)	32 (27 to 40)
Units per kg bodyweight per day	0·53 (0·42 to 0·66)	0·46 (0·41 to 0·58)	0·47 (0·41 to 0·63)
Insulin pump use	15 (60% [39 to 79])	14 (64% [41 to 83])	29 (62% [46 to 75])
Continuous glucose monitoring	4 (16% [4 to 36])	3 (14% [3 to 35])	7 (15% [6 to 28])
Carbohydrate counting	11 (44% [24 to 65])	11 (50% [28 to 72])	22 (47% [32 to 62])
C-peptide (ng/mL)	0·00 (0·00 to 0·02)	0·01 (0·00 to 0·10)	0·00 (0·00 to 0·09)
Modified β-score	0 (0 to 2)	0 (0 to 1)	0 (0 to 1)
0	13 (52% [31 to 72])	13 (59% [36 to 79])	26 (55% [40 to 70])
1	5 (20% [7 to 41])	7 (32% [14 to 55])	12 (26% [14 to 40])
2	6 (24% [9 to 45])	2 (9% [1 to 29])	8 (17% [8 to 31])
3	1 (4% [<1 to 20])	0	1 (2% [<1 to 11])
Clarke score	5·0 (4·0 to 6·0)	4·5 (3·0 to 7·0)	5 (3 to 6)
At least two severe hypoglycaemic events in the year before randomisation	18 (72%)	18 (82%)	36 (77%)

Data are n (%), median (IQR), n/N (%), or n (% [95% CI]).

Table 1: **Baseline characteristics**

and traumatic injury, despite close medical follow-up. We replaced missing C-peptide values at inclusion with values at waiting list registration for four patients in the immediate transplantation group and with the postprandial value for one patient in the insulin group. For one patient in the islet transplantation group, missing fasting glucose value at 6 months after the first injection was replaced with capillary measurement at the same timepoint.

We could not test the interaction between treatment group and randomised strata using logistic regression because no patient in the insulin group had a modified β-score of 6 or higher at 6 months. ANOVA was done with β-score as a continuous variable and showed no interaction (p=0·46). Additionally, the χ^2 test applied by strata showed the same result for the primary outcome regardless of type of patient (p=0·016 for kidney graft recipients [n=9], p<0·0001 for patients with unstable type 1 diabetes [n=38]). Therefore, we combined and analysed all types of patients together.

This trial is registered with ClinicalTrials.gov, number NCT01148680, and is completed.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 8, 2010, and July 29, 2013, 50 patients were randomly assigned to the immediate islet transplantation group (n=26) or to the insulin group (n=24; figure 1). These patients were followed-up until July 4, 2017, when follow-up of the final patient in the insulin group was completed. Three patients did not receive the allocated intervention, so 47 patients were assessed for the primary endpoint. Only 46 patients received islet transplantation because one patient in the insulin group died while on the islet transplantation waiting list. This death was related to prolonged nocturnal hypoglycaemia.

Tables 1 and 2 show characteristics of the patients, pancreas donors, and islet transplants. No major change in use of pump therapy and continuous glucose

	Immediate islet transplantation group (n=25)	Insulin group (n=22)	Total (n=47)
Donor demographics			
Number of donors	63	58	121
Age (years)	51 (45–57)	48 (42–54)	50 (43–55)
BMI (kg/m²)	26·6 (24·0–28·7)	26·1 (22·8–29·4)	26·2 (23·8–29·2)
Sex			
Male	31/63 (49%)	34/58 (59%)	65/121 (54%)
Female	32/63 (51%)	24/58 (41%)	56/121 (46%)
Pancreas cold ischaemia time (h)	6·3 (5·0–7·1)	6·5 (5·3–8·0)	6·3 (5·2–8·0)
Islet transplantation characteristics			
Number of infusions	63	54	117
Total IEQ per infusion	320 667 (259 445–426 511)	327 993 (273 417–377 200)	320 667 (265 842–387 897)
Tissue volume per infusion (mL)	2·3 (1·7–3·2)	2·3 (1·7–3·0)	2·3 (1·7–3·1)
Graft recipients	25 (100%)	21 (95%)*	46 (98%)
Time between registration on waiting list and first infusion (days)	132 (47–327)	374 (177–446)	247 (88–446)
Infusion at 6 months after first infusion			
Total IEQ per kg bodyweight	11 980 (10 464–13 223)	9971 (6086–12 291)	11 324 (9329–13 206)
Number of infusions			
1	3/25 (12% [3–31])	6/21 (29% [11–52])	9/46 (20% [9–34])
2	14/25 (56% [35–76])	9/21 (43% [22–66])	23/46 (50% [35–65])
3	8/25 (32% [15–54])	6/21 (29% [11–52])	14/46 (30% [18–46])
Infusion at 12 months after first infusion			
Total IEQ per kg bodyweight	12 561 (11 390–14 435)	12 631 (11 257–15 355)	12 596 (11 257–14 687)
Number of infusions			
1	2/25 (8% [1–26])	2/21 (10% [1–30])	4/46 (9% [2–21])
2	11/25 (44% [24–65])	8/21 (38% [18–62])	19/46 (41% [27–57])
3	12/25 (48% [28–69])	11/21 (52% [30–74])	23/46 (50% [35–65])

Data are n (%), median (IQR), n/N (%), or n (% [95% CI]), unless otherwise specified. IEQ=islet equivalents. *One patient in this group died while on the islet transplantation waiting list because of prolonged nocturnal hypoglycaemia.

***Table 2*: Donor demographics and islet transplantation characteristics**

monitoring was noted between baseline and 6 months' follow-up in the insulin group (data not shown). Median follow-up was 184 days (IQR 181–186) in the immediate transplantation group and 185 days (172–201) in the insulin therapy group. 40 (87% [95% CI 74–95]) of 46 patients received more than 11 000 IEQ per kg bodyweight; 26 (57% [41–71]) received the target IEQ mass before 6 months and 36 (78% [64–89]) at 12 months.

At baseline, 13 patients in each group had a modified β-score of 0 and no patient had a modified β-score of 6 or higher (table 1). In the immediate transplantation group, 16 (64% [95% CI 43–82]) of 25 patients had a modified β-score of 6 or higher at 6 months after first infusion, whereas none (0% [0–15]) of the 22 patients in the insulin group had a modified β-score of 6 or higher at 6 months after randomisation (p<0·0001). 6 months after the first infusion, eight (32% [15–54]) of 25 patients in the immediate transplantation group had a modified β-score between 3 and 5, whereas 6 months after randomisation, three (14% [3–35]) of 22 patients in the insulin group had a score in this range. The median modified β-score increased significantly from 0 (IQR 0–1) at baseline to 1·5 (0·0–2·0) at 6 months after randomisation in the insulin group (p=0·0091), and from 0 (0–2) at baseline to 6 (5–7) at 6 months in the immediate transplantation group (p<0·0001; figure 2).

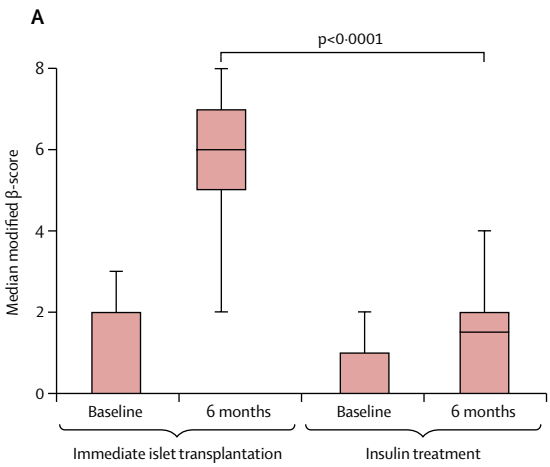
Secondary outcomes at 6 months were assessed in the same population as was the primary outcome. HbA_{1c} was reduced in the immediate transplantation group compared with the insulin group at 6 months (HbA_{1c} was 5·6% [38 mmol/mol] in the islet transplantation group *vs* 8·2% [66 mmol/mol] in the insulin group at 6 months; p<0·0001; figure 3). No difference in fasting glycaemia was observed between the groups: 5·9 mmol/L (IQR 5·2–6·7) in the immediate transplantation group versus 5·7 mmol/L (4·9–10·9) in the insulin group (p=0·92). 21 (84% [95% CI 64–96]) of 25 patients in the immediate transplantation group had an HbA_{1c} of less than 7% without severe hypoglycaemia, compared with no (0% [0–15]) patient in the insulin group (p<0·0001; figure 3). The median number of severe hypoglycaemic events per year was zero (IQR 0–0) in the immediate transplantation group compared with two (0–4) in the insulin group (p<0·0001). The median number of

non-severe hypoglycaemic events was zero (0–0) in the immediate transplantation group versus five (0–17) in the insulin group (p=0·0003). 23 (92% [95% CI 74–99]) patients in the immediate transplantation group were free from severe hypoglycaemia versus eight (36% [17–59]) in the insulin group (p<0·0001).

Change in insulin requirements and basal C-peptide concentrations are shown in figure 3. Insulin independence was achieved in 11 (44% [24–65]) of 25 patients in the immediate transplantation group 6 months after the first infusion (p=0·0004). Results of the Diabetes Quality of Life questionnaire are shown in figure 4, and those of the SF-36 are reported in the appendix. All items of the Diabetes Quality of Life questionnaire except for wellbeing and social worry were significantly improved in the immediate transplantation group at 6 months after first infusion compared with the insulin group at 6 months after randomisation (figure 4). On the SF-36, general health perceptions and health transition were significantly improved in the immediate transplantation group compared with the insulin group (p=0·008 for general health and p=0·0006 for health transition; appendix).

Total median cost at 6 months per patient for the immediate transplantation group was €52 240 (46 392–77 506), including €4641 (3855–5651) for pancreas procurement, €33 568 (29 851–52 210) for islet isolation, €7751 (6981–10 471) for hospital stay, €5612 (4177–7984) for medication (including €5208 [3055–7220] for immunosuppressive drugs), and €1009 (3·84–4520) for in-hospital follow-up. Total median cost per patient for the insulin group was €184·99 (48·00–699·63).

The 12 month outcomes were assessed in the 46 patients who had received islet transplantation and were alive at 12 months, and were compared with the entire cohort at baseline (n=47; table 1). Median follow-up for these 46 patients was 368 days (364–373). At 12 months after the first infusion, 29 (63% [95% CI 48–77]) of 46 patients had a modified β-score of 6 or higher (p<0·0001 *vs* baseline); the median modified β-score was 7 (5–8; p<0·0001 *vs* baseline). 43 (93% [82–99]) patients had a functioning graft with a median HbA_{1c} of 5·8% (IQR 5·5–6·7; p<0·0001 *vs* baseline; figure 5), and median fasting glycaemia was 5·7 mmol/L (5·2–7·3; p=0·0002 *vs* baseline). 32 (70% [95% CI 54–82]) of 46 patients had an HbA_{1c} of less than 7% without severe hypoglycaemia, compared with only one (2% [0–11]) of 47 patients at baseline (p<0·0001; figure 5). 37 (80% [66–91]) of 46 recipients had reached an HbA_{1c} of less than 7%. The median number of severe hypoglycaemic events per year was zero (IQR 0–0) at 12 months versus two (0–4) at baseline (p<0·0001). The median number of non-severe hypoglycaemic events that the patient was aware of was zero (0–0) at 12 months versus ten (4–17) at baseline (p<0·0001). 39 (85% [95% CI 71–94]) of 46 patients were free from severe hypoglycaemia at 12 months after transplantation compared with 16 (34% [21–49]) of 47 at baseline (p<0·0001).



B

Breakdown of modified β-score	Immediate islet transplantation patients (n=25)	Insulin-treated patients (n=22)
0	0	7 (32%)
1	0	4 (18%)
2	1 (4%)	8 (36%)
3	4 (16%)	1 (5%)
4	0	2 (9%)
5	4 (16%)	0
6	5 (20%)	0
7	6 (24%)	0
8	5 (20%)	0

Figure 2: **Median modified β-score at baseline and 6 months**
(A) Data are median and IQR. The modified β-score was assessed in the immediate islet transplantation group at baseline and 6 months after islet transplantation and in the insulin group at baseline and 6 months after randomisation. (B) Data are n (%). Breakdown of the modified β-score in the immediate islet transplantation group 6 months after islet transplantation compared with in the insulin group 6 months after randomisation.

MAGE index and insulin requirement were reduced at 12 months compared with baseline (figure 4). Hypoglycaemia awareness was restored, with a median Clarke score of 0 (IQR 0–2) at 12 months after first islet transplantation (p<0·0001 *vs* baseline).

27 (59% [43–73]) of 46 recipients were insulin independent 12 months after first transplantation (p<0·0001 *vs* baseline). In separate analysis of the randomised groups, no difference in metabolic outcomes (HbA_{1c}, C-peptide, insulin requirement, insulin independence, occurrence of severe hypoglycaemia) was noted between kidney graft recipients and patients with unstable type 1 diabetes (data not shown).

Analysis of the β-2 score showed that it was consistent with the modified β-score. At 6 months, 18 (72% [95% CI 51 to 88]) of 25 immediate islet recipients had a β-2 score of 15 or higher and 20 (80% [59 to 93]) of 25 had a β-2 score of 10 or higher. No patients in the insulin group had a β-2 score of 10 or higher (p<0·0001). At 12 months, 39 (85% [71 to 94]) of 46 recipients had a β-2 score of 10 or higher and 34 (74% [59 to 86]) had a β-2 score of 15 or higher versus one (2% [<1 to 11]) of 47 patients at baseline (both p<0·0001).

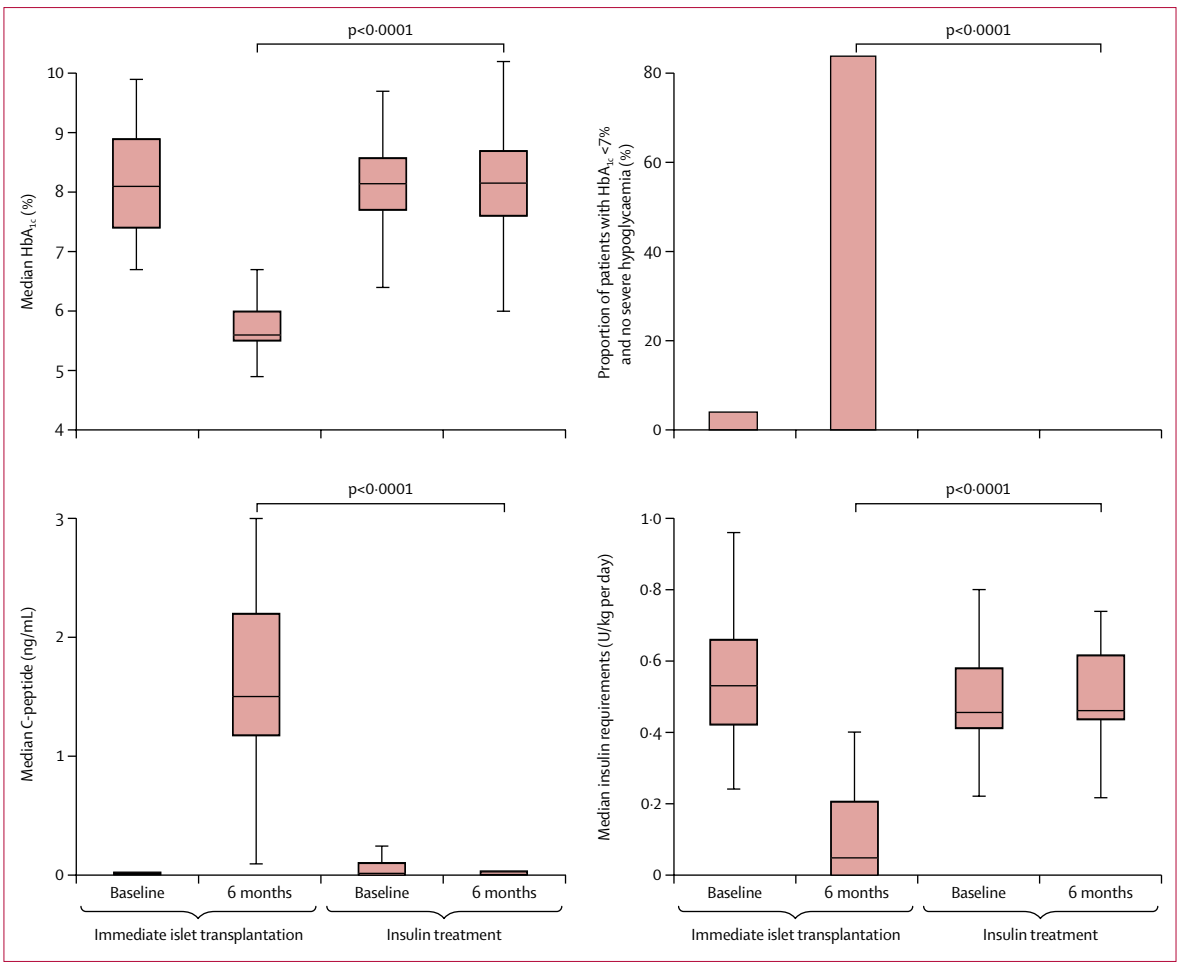


Figure 3: **Metabolic outcomes at baseline and 6 months**
Boxes show IQRs, with bands within the boxes indicating medians. The error bars indicate ranges. Metabolic outcomes were assessed at baseline and 6 months after islet transplantation in the immediate islet transplantation group and at baseline and 6 months after randomisation in the insulin group.

135 SAEs were reported between randomisation and 12 months after first islet transplantation. The most common SAEs are shown in table 3, and details of the SAEs are in the appendix. Ten SAEs related to diabetes complications or intercurrent diseases were reported in patients in the insulin group between baseline and first islet infusion. One death from cardiac arrest related to prolonged nocturnal hypoglycaemia was reported in the insulin group while the patient was on the islet transplant waiting list. In the immediate transplantation group, 11 SAEs were reported between inclusion and first islet infusion and 41 in the first 6 months after islet infusion. Frequent SAEs were digestive disorders, cytopenia, and infectious disease. At 6 months, four (7%) of 55 islet infusions in three of 25 patients in the immediate transplantation group were associated with bleeding complications. One patient described transient cardiac arrest after an islet infusion complicated with a haemorrhage. 114 SAEs occurred in the entire cohort at 12 months after first infusion. Seven (6%) of 111 islet infusions in six of 46 recipients were complicated with a haemorrhage. One portal vein thrombosis was reported. 14 of 46 patients were positive for HLA antibodies 12 months after islet transplantation, compared with two patients at baseline. At 6 months, the glomerular filtration rate was decreased in patients transplanted with islets alone compared with patients who had previously received a kidney graft (appendix). At 12 months after the first islet infusion, the median glomerular filtration rate was decreased in all islet recipients, from 90·5 mL/min (IQR 76·6–94·0) to 71·8 mL/min (59·0–89·0) in recipients who had not previously received a kidney graft and from 63·0 mL/min (55·0–71·0) to 57·0 mL/min (45·5–65·1) in recipients who had previously received a kidney graft.

Discussion

In the TRIMECO trial, 16 (64%) of 25 patients assigned to immediate islet transplantation had a modified β-score of 6 or higher at 6 months after first islet infusion compared with none in the insulin group at 6 months after randomisation. Additionally, 24 (96%) of the 25 patients in the immediate islet transplantation group

had a functioning islet graft, 21 (84%) had an HbA_{1c} level of less than 7%, and 23 (92%) were free from severe hypoglycaemia. Moreover, 12 months after first islet infusion, 29 (63%) of the 46 transplantation recipients in the overall study cohort had a modified β-score of 6 or higher. Insulin independence was achieved in 27 (59%) of these patients, which was consistent with previous findings.[3] Quality of life was improved after islet transplantation, which was also consistent with data from previous non-controlled studies.[5,20] Although studies with longer-term follow-up are needed, our findings suggest that islet transplantation is a valid option for patients with severe, unstable type 1 diabetes who are not responding to intensive medical treatments.

Although criteria defining islet transplantation success remain debated,[4,17,21] its effectiveness in restoring glycaemic stability, even with partial graft function, led several previous studies[22,23] to propose islet transplantation as an option for patients with type 1 diabetes with severe hypoglycaemia. The ADA[24] recommends a stepped-care approach for patients with severe hypoglycaemia based on a less stringent HbA_{1c} target (<8%), participation in structured educational programmes about flexible insulin therapy and a psychoeducational programme to restore hypoglycaemia awareness,[25] and use of technologies such as sensor-augmented pump therapy or a predictive low-glucose management device. However, 29 (62%) of the 47 patients enrolled in our study were unable to avoid severe hypoglycaemia, despite being treated with pump therapy and having received medical and educational management, suggesting that the stepped-care approach might be insufficient for some patients with severe metabolic profiles.

The incidence of severe hypoglycaemia was lower in our population than in the population described by Hering and colleagues,[3] which is probably explained by the fact that the median HbA_{1c} value at baseline was higher in our population (8·1% [65 mmol/mol] *vs* 7·2% [55 mmol/mol]). This difference is probably due to our use of a less stringent target for HbA_{1c} to avoid hypoglycaemic events.

135 SAEs occurred during our study, of which 92 were in the 6 months after first islet infusion. One patient died from severe hypoglycaemia while on the waiting list for islet transplantation, showing the metabolic severity of the study population. Immunosuppression was responsible for two-thirds of the SAEs, with no unexpected adverse events related to immunosuppression. Bleeding complications were associated with 6·3% of islet infusions, which was lower than the frequency reported in a previous study.[3] However, bleeding complications can be severe, as evidenced by the patient in our study who had a transient cardiac arrest after an islet infusion complicated by a haemorrhage. Consistent with previous studies,[26,27] we noted a decrease in glomerular filtration rate after islet transplantation, mainly due to calcineurin inhibitor therapy and reduction of hyperfiltration driven by the improvement in glycaemic control. A careful analysis of renal function is required before islet transplantation, and candidates should be informed of the risks of islet transplantation before

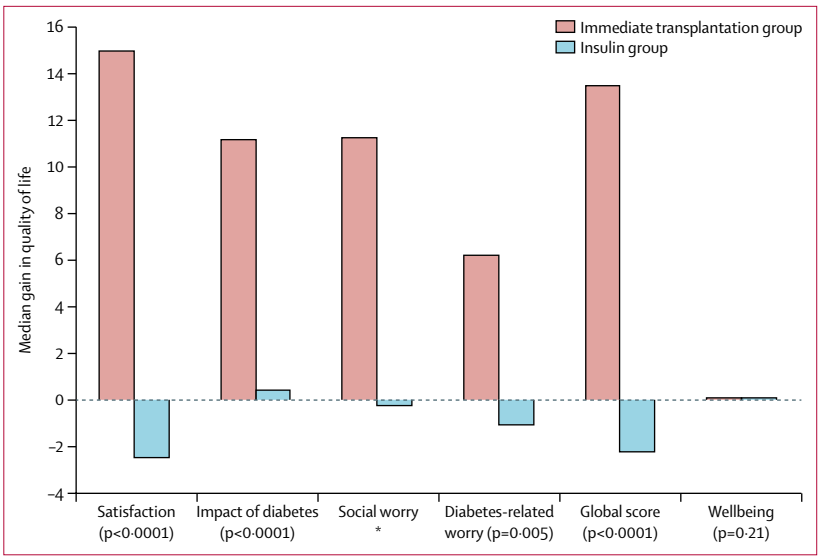


Figure 4: **Median gain in quality-of-life dimensions assessed with the Diabetes Quality of Life questionnaire**
Quality of life was assessed at 6 months after first islet infusion in the immediate transplantation group and at 6 months after randomisation in the insulin group and compared with baseline. *No statistical tests were applied because of the low number of respondents to this item.

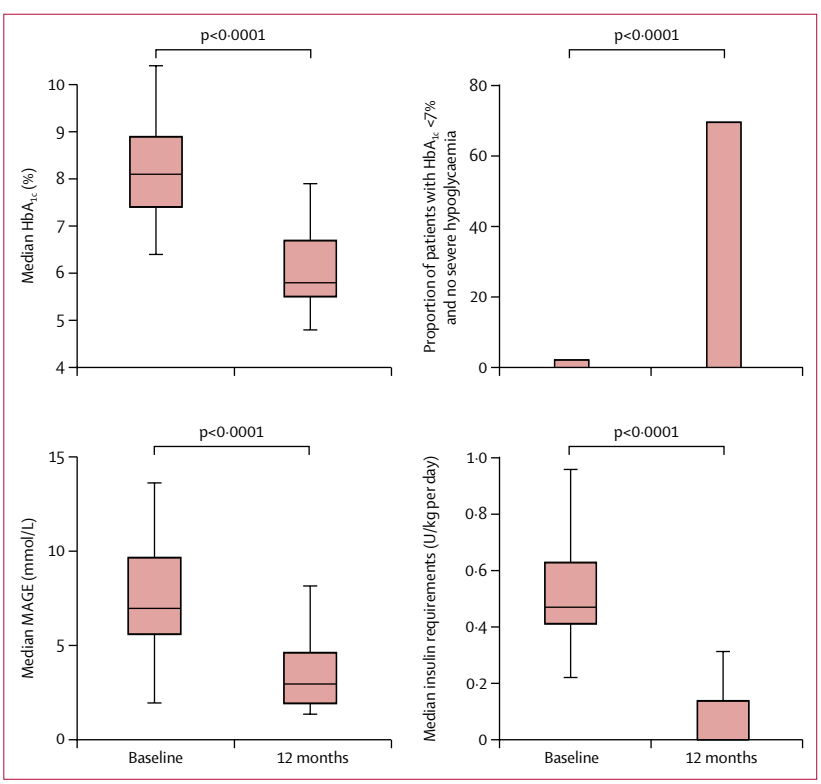


Figure 5: **Outcomes in the entire cohort at 12 months after first islet transplantation**
Boxes show IQRs, with bands within the boxes indicating medians. The error bars indicate ranges. MAGE=mean amplitude of glycaemic excursions.

	Immediate islet transplantation group			Insulin group				Total (n=46)*
	Waiting list for transplantation (n=25)	First infusion to 6 months (n=25)	6–12 months after first infusion (n=25)	Baseline to 6 months after randomisation (n=22)	Waiting list for transplantation (n=22)	First infusion to 6 months (n=21)*	6–12 months after first infusion (n=21)*	
Infections and infestations	0	5 (20%)	4 (16%)	1 (5%)	2 (10%)	4 (19%)	4 (19%)	20 (43%)
Gastrointestinal disorder	0	7 (28%)	4 (16%)	0	0	6 (29%)	1 (5%)	18 (39%)
Blood and lymphatic system disorders	1 (4%)	5 (20%)	3 (12%)	0	0	7 (33%)	0	16 (35%)
Procedural complication	0	5 (20%)	0	0	0	4 (19%)	0	9 (20%)
Nervous disorders	2 (8%)	2 (8%)	0	0	0	2 (10%)	2 (10%)	8 (17%)
Renal and urinary disorders	2 (8%)	1 (4%)	0	0	0	3 (14%)	0	6 (13%)
Cardiac disorders	0	1 (4%)	0	0	2 (10%)	2 (10%)	0	5 (11%)
Metabolism and nutrition disorders	0	1 (4%)	1 (4%)	0	2 (10%)	2 (10%)	2 (10%)	6 (13%)

Data are number of patients (%). Serious adverse events that occurred in more than 10% of patients in either group are reported. *Number of patients differs from baseline because one patient in the insulin group died while on the islet transplantation waiting list.

Table 3: **Serious adverse events**

undergoing the procedure. Notably, a high proportion of patients in our study had HLA sensitisation, which could be a barrier to further transplantation in the future.

We prospectively collected cost data, allowing a real-life estimation of the cost of islet transplantation. This approach differed from other health economic studies of islet transplantation,[28] which estimated costs using modelling. We found that the cost per patient was substantially higher for the immediate transplantation group at 6 months after first islet infusion than for the insulin group at 6 months after randomisation. Thus, the short-term costs generated by islet transplantation and side-effect management might outweigh the benefits of improved metabolic control. However, these cost data should be interpreted with caution because they only represents the hospital perspective and a broader provider perspective is needed to obtain a global cost of islet transplantation versus insulin therapy. A cost analysis with longer follow-up is planned in the randomised STABILOT study (NCT02854696),[29] which is expected to be completed in 2021.

Our study has some limitations. First, recommendations and available technologies have changed since 2009, when the TRIMECO study was designed, and few patients in our study were using real-time continuous glucose monitoring or other modern technologies for the management of hypoglycaemia unawareness or severe hypoglycaemia. Nevertheless, although real-time continuous glucose monitoring has shown efficacy in prevention of severe hypoglycaemia,[30] no study has assessed the efficacy of predictive low-glucose management devices in preventing such events in high-risk patients. Future studies will need to identify the benefits of these technologies in this population, particularly in comparison with islet transplantation. This issue will be addressed in the STABILOT study.

Second, our approach to management of the insulin group might be considered as a limitation. Given that optimised self-management with educational, therapeutic, and technological support has been shown to improve outcomes for patients with hypoglycaemia unawareness,[31] closer follow-up of the patients treated with insulin might have been more suitable. Nevertheless, the rate of severe and non-severe hypoglycaemia was reduced in the insulin group at 6 months compared with baseline without an increase in HbA_{1c} level. This finding suggests that the approach to management in the insulin group in our study was effective in improvement of metabolic outcomes.

Third, the open-label design of the study might have caused some bias: patients in the insulin group were informed that they would be put on the transplantation waiting list 6 months after randomisation, which might have decreased their compliance with insulin therapy. However, the improvement in metabolic outcomes in the insulin group at 6 months after randomisation suggests that patients were invested in their medical treatment.

The assessment of islet transplantation efficacy at 6 months was a short-term evaluation. Nevertheless, we judged that a longer delay for the insulin group would have been unethical because of the severe metabolic profile of the study participants. Long-term evaluation of islet transplantation to analyse the balance of risks and benefits should be done in a randomised trial in the future.

Use of a modified β-score as primary endpoint could be considered as a limitation, given that patients in the control group would be unable to obtain a modified β-score of 6 or higher. However, the modified β-score permitted a composite analysis of HbA_{1c}, fasting glycaemia, and insulin requirement in the insulin group, which is not possible with the classic β-score, in which negativity for C-peptide overwhelms the score. Although patients who have not received an islet transplant cannot have a modified β-score of 6 or higher, we did note scores between 3 and 5 in three (14%) of 22 patients in the insulin group 6 months after randomisation owing to improvements in HbA_{1c} and glycaemia and modification of insulin dose through intensive medical management.

Therefore, the modified β-score permitted the effects of islet transplantation to be distinguished from those of intensive medical management in the improvement of metabolic outcomes.

In conclusion, the results of the TRIMECO trial suggest that, compared with insulin therapy, islet transplantation is an effective intervention in patients with severe forms of type 1 diabetes. We suggest that islet transplantation should be integrated into the stepped-care approach for the treatment of such patients. However, studies with longer follow-up and health economic analyses are needed to determine the long-term effectiveness of this procedure and its cost-effectiveness over longer periods. Meanwhile, because of its acceptable safety profile, islet transplantation should be considered as a possible option when diabetes management strategies are ineffective in preventing severe hypoglycaemia.

Contributors

SLa contributed to patient follow-up, data interpretation, figure conception, and writing of the report. M-CV contributed to study design, patient enrolment, data interpretation and analysis, and writing of the report. LK, AW, SB, and CT contributed to study design, patient enrolment, data interpretation, and writing of the report. SG contributed to patient enrolment and writing of the report. DB contributed to study design and islet isolation. J-LB, CC, ER, AP, EM, and TB contributed to study design, data interpretation, and writing of the report. RT, FB, and KB contributed to patient follow-up. SLo contributed to data safety management. JK-C and HE contributed to islet isolation. KS contributed to figure construction and the statistical analysis. GG and CC-B contributed to the cost analysis. LB contributed to study design, patient follow-up, and organ procurement. FP contributed to study design and data interpretation. P-YB contributed to study design, patient enrolment and follow-up, data interpretation, and writing of the report.

Declaration of interests

We declare no competing interests.

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