



Islet-after-kidney transplantation versus kidney alone in kidney transplant recipients with type 1 diabetes (KAIK): a population-based target trial emulation in France

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Summary

Background Islet transplantation has been associated with better metabolic control and quality of life than insulin treatment alone, but direct evidence of its effect on hard clinical endpoints is scarce. We aimed to assess the effect of islet transplantation on patient-graft survival in kidney transplant recipients with type 1 diabetes.

Methods In this retrospective cohort study, we enrolled all patients with type 1 diabetes who received a kidney graft in France during the study period, identified from the CRISTAL nationwide registry. Non-inclusion criteria included recipients from transplant centres that never proposed islet transplantation during the study period, recipients with a functional pancreas throughout the follow-up duration, recipients with more than two kidney transplants, HLA-sensitised recipients, recipients with less than 1 year of follow-up after kidney transplantation, misclassified recipients with type 2 diabetes, recipients aged over 65 years, recipients of kidney grafts from Donation after Circulatory Death donors, recipient with HIV or hepatitis, recipients with cancer, and recipients of combined liver-kidney transplants. Patients who also received islet-after-kidney (IAK) transplantation were compared with controls who received kidney transplantation alone according to a 1:2 matching method based on time-dependent propensity scores, ensuring patients comparability at the time of islet transplantation. The primary outcome was patient-graft survival, a composite outcome defined by death, re-transplantation, or return to dialysis.

Findings Between Jan 1, 2000, and Dec 31, 2017, 2391 patients with type 1 diabetes were identified as having received a kidney transplant, 47 patients of whom also received an islet transplantation. 2002 patients were not eligible for islet transplantation and 62 were excluded due to missing data. 327 eligible recipients from 15 centres were included in the study dataset for the target trial emulation. 40 patients who received IAK transplantation were successfully matched to 80 patients who received kidney transplantation alone. 13 (33%) of 40 patients in the IAK transplantation group returned to dialysis or died, compared with 36 (45%) of 80 patients in the kidney transplantation alone group. We found a significant benefit of islet transplantation compared with kidney transplantation alone on patient-graft survival, with a hazard ratio (HR) of 0.44 (95% CI 0.23–0.88; $p=0.022$), mainly explained by a protective effect on the risk of death (HR 0.41, 0.13–0.91; $p=0.042$). There was no meaningful association between IAK and death-censored graft survival (0.73, 0.30–1.89; $p=0.36$).

Interpretation In kidney transplant recipients with type 1 diabetes, IAK transplantation was associated with a significantly better patient-graft survival compared with kidney transplantation alone, mainly due to a protective effect on the risk of death. These results potentially serve as compelling grounds for advocating wider access to islet transplantation in patients with type 1 diabetes undergoing kidney transplant, as reimbursement of islet transplantation is provided in few countries worldwide.

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Introduction

Allogeneic transplantation of pancreatic islets represents a validated strategy for β -cell replacement in the treatment landscape for type 1 diabetes.¹ Islet transplantation involves infusion of pancreatic islets into the portal vein, aiming to restore endogenous insulin secretion. Notably,

the efficacy of islet transplantation in achieving glycaemic control has been established through prospective clinical trials spanning the past two decades.^{2–5} Access to this technique is scarce, with reimbursement available in few countries.^{6,7} Where available, the indications for islet transplantation are extended to narrow categories of recipients:

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Research in context

Evidence before this study

By contrast with insulin-based treatment, islet transplantation emerges as an efficacious strategy for managing metabolic control. However, there is a paucity of long-term mortality data comparing islet transplantation against control cohorts, especially in patients with type 1 diabetes and a kidney transplant. We searched in PubMed and Embase databases from Jan 1, 2000, to Dec 2023, using the search terms “islet transplantation” AND “kidney transplantation” for articles in English. We identified two studies published by the same group: the first study compared islet-after-kidney recipients to kidney transplantation alone recipients with type 1 diabetes, and the second study compared successful islet-after-kidney recipients versus unsuccessful islet-after-kidney recipients. In both studies, islet transplantation was associated with better long-term outcomes, but meaningful discrepancies existed in baseline characteristics between the groups. Consequently, the primary objectives of our study encompassed the emulation of a comprehensive nationwide target trial, comparing individuals with type 1 diabetes who received islet transplantation after

islet transplantation alone is available to individuals with type 1 diabetes and severe hypoglycaemia and islet transplantation can be given with kidney transplantation in patients with type 1 diabetes and end-stage renal disease. Distinct from islet transplantation alone, in which the introduction of immunosuppressive treatment could affect prognosis, patients who receive islet transplantation after kidney transplant—already under established immunosuppressive protocols—present an appropriate population for examining the intrinsic effect of islet transplantation on clinical outcomes. Previous observational studies suggested a potential benefit of islet transplantation in kidney transplantation.^{8,9} However, it is important to robustly demonstrate its benefit on hard clinical endpoints such as kidney graft failure or mortality, thereby bolstering the equitable availability of this treatment. We report the results of the kidney transplantation alone versus islet-after-kidney (KAIK) study, a comprehensive target emulation trial evaluating the effect of islet-after-kidney (IAK) transplantation on patient-graft survival in patients with type 1 diabetes with a kidney transplant, compared with kidney transplantation alone.

Methods

Study design and patients

This retrospective cohort study was formulated through a two-step approach. First, we identified all adults diagnosed with type 1 diabetes who underwent kidney transplantation in France during the study period. Patients were identified from the CRISTAL nationwide comprehensive registry maintained by the Agence de la Biomédecine (the National Agency overseeing the French Allocation system) which is mandatory for each

kidney transplantation with those treated with kidney transplantation alone, and to analyse how these interventions influenced the risks of mortality and return to dialysis.

Added value of this study

We found a significant association between islet transplantation and a reduced hazard of death or return to dialysis in kidney transplant recipients with type 1 diabetes. This resulted in a significant increase in both life expectancy with a functioning graft and the overall life expectancy in patients treated with islet-after-kidney transplantation. After 1:2 matching, we found a significant benefit of islet transplantation on patient-graft survival (with graft failure defined as return to dialysis, re-transplantation, or death).

Implications of all the available evidence

These results potentially serve as compelling grounds for advocating wider access of islet transplantation, as reimbursement of islet transplantation is currently provided in only few countries worldwide.

allogeneic transplantation recipient in France. The termination point for our follow-up analysis was Dec 31, 2021. The initial study population gathered all patients with type 1 diabetes who received a kidney transplant during the study period in one of the 35 French centres that performed renal transplantation. We then enrolled into the intermediate population all patients from the 15 centres from which at least one patient received an islet transplantation during the study period. Islet transplantation itself was performed in eight centres, therefore some patients received islet transplantation in a different centre than the one in which they received kidney transplantation. However, these patients were followed up before and after the islet transplantation in their kidney transplant centre. Within this framework, an array of variables pertinent to donors, recipients, and the transplantation procedure itself were compiled and is listed in the appendix (p 5).

To replicate the conditions of a target trial, each control participant integrated into the matching process was required to uphold the positivity hypothesis. This concept indicated that each participant should exhibit a non-zero chance of undergoing islet transplantation—a criterion inherently defining non-inclusion. Subsequently, specific characteristics that were never observed in the IAK transplantation population were identified and applied within the dataset as non-inclusion criteria. Non-inclusion criteria included recipients from transplant centres that never proposed islet transplantation during the study period, recipients with a functional pancreas throughout the follow-up duration, recipients with more than two kidney transplants, HLA-sensitised recipients, recipients with less than 1 year of follow-up after kidney transplantation,

misclassified recipients with type 2 diabetes, recipients aged over 65 years, recipients of kidney grafts from Donation after Circulatory Death donors, recipient with HIV or hepatitis, recipients with cancer, and recipients of combined liver-kidney transplants.

The dataset resulting from this two-step process subsequently underwent a comprehensive nationwide prospective data collection endeavour. This undertaking aimed to verify the diagnosis of type 1 diabetes, defined by a fasting C-peptide level below 0.3 ng/ml. Additionally, the data collection aimed to ensure minimal missing data. Longitudinal data was gathered, including post-transplant serum creatinine concentration; HbA_{1c}; bodyweight measurements; and occurrences of cardiovascular events such as stroke, heart attacks, and acute ischaemic limb episodes. Moreover, relevant information specific to the the IAK transplantation population were collected. All the variables collected are listed in the appendix (p 5). Finally, all patients who lacked at least one missing value for covariates included in the matching process were excluded from the final study population and target trial analysis.

The study protocol adhered to French laws. These measures involved approval, pseudonymisation, and protective measures in accordance with Agreement No. DR-2020-062 issued by the Commission Nationale de l'Informatique et des Libertés (the National Commission on Informatics and Liberties). Protocol approval was granted by the local institutional review board under number DEC19-483. Participants' informed non-opposition was obtained for their participation in the study as requested by French regulatory authorities.¹⁰ The study was conducted in adherence to the principles outlined in the Istanbul Declaration and the Helsinki Declaration.

Procedures

The main study intervention was islet transplantation, consisting of up to three sequential islet infusions, performed within a total period of 6 months, with the aim of reaching adequate metabolic control without exogenous insulin.² All recipients who underwent at least one islet transplantation in the course of their post-kidney transplant follow-up were enrolled into the IAK transplantation group at the time of the first islet transplantation. Subsequently, we performed a target trial to compare participants in the IAK transplantation group with matched counterparts who had exclusively received a kidney transplant at the time of matching (kidney transplantation alone group).

Outcomes

The study primary outcome was patient-graft survival, meaning death-uncensored kidney graft survival. This composite outcome, commonly reported in kidney transplantation,¹¹ is defined as the occurrence of death, re-transplantation, or return to dialysis. Secondary outcomes were the probability of death-censored graft

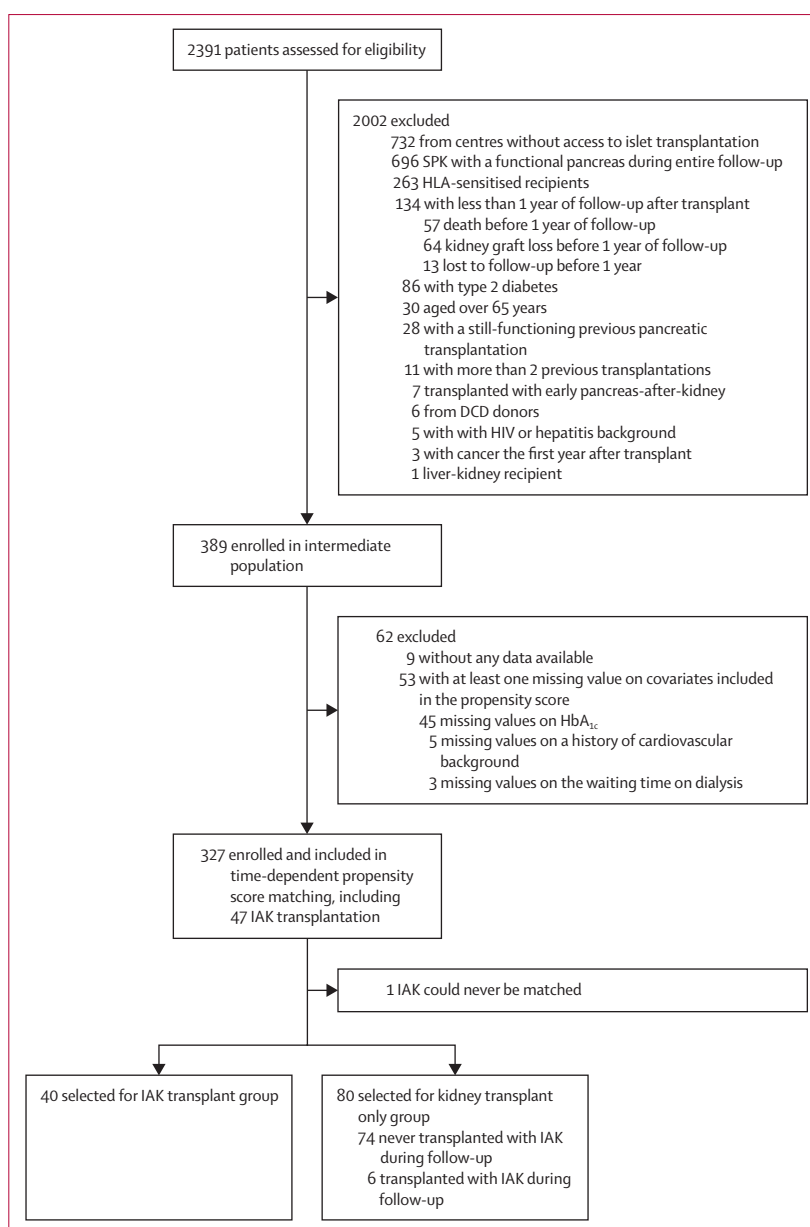


Figure 1: Trial profile

SPK=simultaneous pancreas-kidney transplantation. DCD=donation after circulatory death; IAK=islet-after-kidney.

survival (the probability of returning to dialysis or requiring re-transplantation, in which death while being transplanted is not considered as graft failure), and patient survival (the probability of death regardless of the kidney transplantation status).

Statistical analysis

Baseline variables were described by median (IQR) for continuous variables and effective (frequency) for categorical variables. The Aalen-Johansen hazard ratio (HR) estimator, a multi-state version of the Kaplan-Meier estimator for the risk of a survival process, was used to

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See Online for appendix

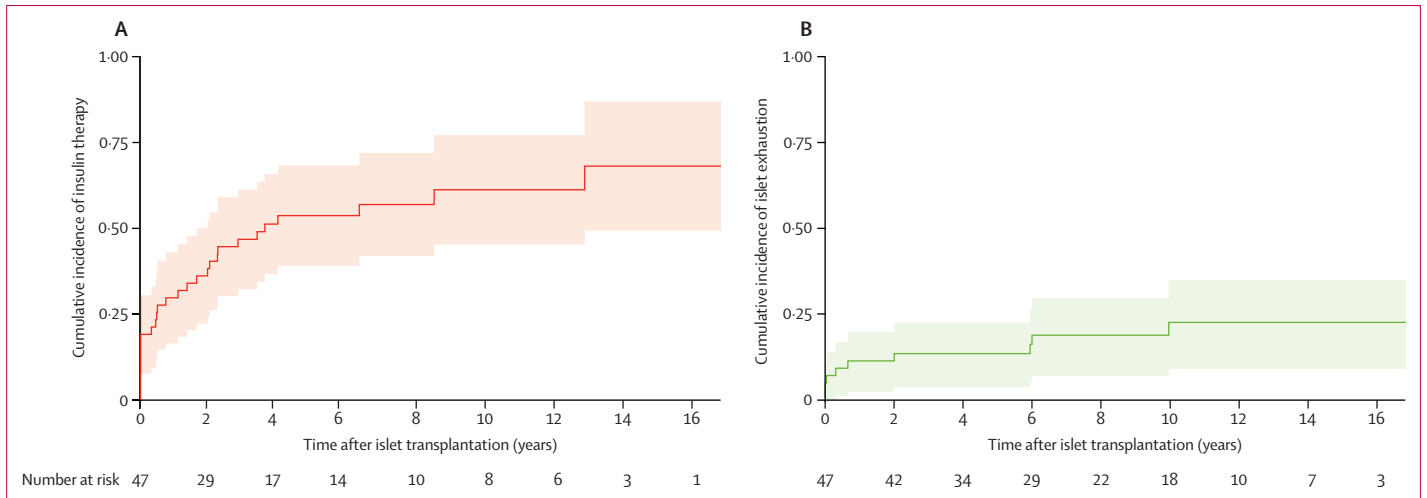


Figure 2: Cumulative incidences of insulin requirement and islet graft exhaustion after islet transplantation

Shaded areas indicate 95% CI. (A) Cumulative incidence of insulin requirement after islet transplantation in patients after IAK transplantation. (B) Cumulative incidence of islet graft exhaustion (fasting c-peptide below 0.3 ng/mL) after islet transplantation in patients after IAK transplantation. Data was determined using the Aalen-Johansen estimator. IAK=islet-after-kidney.

describe the cumulative incidence of insulin requirement and islet graft exhaustion (ie, the probability of a fasting C-peptide below 0.3 ng/mL after islet transplantation) in IAK transplantation patients, in which death acts as a competing risk to their respective incidence.

In line with the study's primary objective, we adopted a time-dependent propensity score matching approach.¹² This strategy allowed us to circumvent immortality bias and accurately evaluate the population-level effect by considering time-varying confounders. The applicability of this method within the context of kidney transplantation has been previously described¹³ and is depicted in the appendix (p 7). Time-dependent propensity scores were estimated using the linear predictor derived from a cause-specific Cox model. For this step, the kidney transplantation date established the origin and start of the observational period for each patient, providing a reference time from which we calculate the time elapsed between kidney transplantation and islet transplantation (the event of interest). Of note, this analysis also considered the competitive risk of death, kidney graft loss, or end of follow-up.

Log linearity and proportional hazards assumptions were tested both graphically (log-minus-log method and Schoenfeld residuals, respectively) and numerically (by comparing a linear model and a model with splines and by using a score test, respectively). Potential confounders, linked with the likelihood of islet transplantation and the risk of death or return to dialysis, were identified through the construction of two separate directed acyclic graphs. This process was executed under the purview of a double-blinded adjudication by two distinct experts in the field (appendix pp 12–15). Minimally sufficient sets of confounders were established with the Dagitty software version 3.1 (<https://www.dagitty.net/>).

When evaluating the risk of death, considered covariates were recipient age, time spent on dialysis, HbA_{1c}, serum creatinine, cardiovascular disease presence, recipient BMI, and the year of transplantation. For assessing the risk of returning to dialysis, considered covariates were donor type, donor age, cold ischaemia time, recipient age, time spent on dialysis, HbA_{1c}, serum creatinine, cardiovascular disease presence, recipient BMI, and the year of transplantation. HbA_{1c}, serum creatinine, cardiovascular disease, and recipient BMI were considered as longitudinal data. The centre effect was not considered in the propensity score analysis, as the number of centres involved would have resulted in an imbalance between the groups. To mitigate this potential bias between centres, enrolment was limited to the 15 centres from which at least one patient received islet transplantation during the study period.

Once propensity scores were estimated, they were employed to match IAK transplantation recipients with similar kidney transplantation alone recipients who were eligible for transplantation at the same time after kidney transplantation, using a 1:2 matching ratio,¹⁴ with IAK transplantation as the target of causal inference. The nearest neighbour matching with calliper algorithm was used, setting a maximum calliper of 20% of the SD of the linear predictor.¹⁵ The balance of selected covariates between the two groups was assessed through standardised mean differences, with an absolute standardised difference exceeding 10% indicating substantial imbalance.¹⁶

Within the subcohort resulting from the matching process, the matching time was considered as the target trial baseline. This corresponded with the initial islet transplantation time in the IAK transplantation group and to the time at which an IAK transplantation could have taken place but did not actually occur in the

control kidney transplantation alone group. From this baseline, we estimated patient and graft survivals with the Kaplan–Meier estimator, and computed the corresponding restricted mean survival time through area under the curve calculations. The target trial was intended to emulate a randomised trial with intention-to-treat analysis. Any recipient in the control group transplanted with islets after matching was thus not censored at the time of islet transplantation. Because the matching was a random process, we performed 1000 bootstrap samples from 327 participants, and performed the matching on the 1000 bootstrap samples and propensity score calculation: the results corresponded to the median of the estimations and 95% CIs were computed with the 2.5th and 97.5th percentiles. Survival curves were also built by bootstrapping considering the mean survival in each group and at each timepoint.^{17,18} All analytical procedures were done using R, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 2000 and Dec 31, 2017, 2391 recipients registered as having type 1 diabetes underwent kidney transplantation in 31 centres in France. 2002 patients were not eligible for islet transplantation and 62 were excluded due to missing data. 327 eligible recipients from 15 centres were included in the study dataset for the target trial emulation (figure 1). Most exclusions were due to recipient from centre without access to islet transplantation (n=732), simultaneous pancreas–kidney transplantation with functional pancreas for entire follow-up (n=696), or HLA sensitised (n=263). Baseline characteristics were similar between groups (appendix p 18). Median recipient age was 44.3 years (IQR 35.9–51.7) and median recipient BMI was 22.4 kg/m² (20.6–25.1). 203 (62%) of 327 patients were male. 161 (49%) of 327 participants initially received a simultaneous pancreas and kidney transplantation but lost their pancreas graft, within a median of 10.0 days (IQR 2.0–573.0) after transplantation. 316 (97%) kidney transplant recipients were treated with a combination of tacrolimus and mycophenolate mofetil. No patients were initially treated with mTOR inhibitors. By contrast, islet transplantation involved a switch of mycophenolate mofetil to sirolimus in 25 (53%) of 47 patients in the IAK transplantation group.

47 (14%) of 327 recipients with confirmed type 1 diabetes underwent IAK transplantation during follow-up. The median duration between kidney transplantation and the first islet infusion was 35.4 months (IQR 22.1–49.2). During the study period, 5 (11%) of 47 patients received one islet infusion, 26 (55%) received

	Kidney alone (N=80)	Islet-after- kidney (N=40)	Standardised differences (%)
Variables selected for matching			
Recipient age (years)*	46.2 (8.8)	46.1 (8.8)	0.5
Sex			
Male	46 (58%)	23 (58%)	0.0
Female	34 (43%)	17 (43%)	0.0
Recipient BMI (kg/m ²)*	23.0 (3.7)	22.8 (2.6)	6.4
Serum creatinine (mg/dL)*	1.3 (0.5)	1.3 (0.3)	9.4
eGFR (MDRD)	66.1 (23.5)	64.6 (16.7)	7.3
History of cardiovascular disease background*	21 (26%)	10 (25%)	2.3
Kidney transplantation after 2010	17 (21%)	7 (18%)	7.9
Time spent on dialysis (years)	1.7 (2.2)	1.7 (1.7)	0.2
Recipient HbA _{1c} (%)*	7.9 (1.5)	7.8 (1.3)	7.9
Recipient HbA _{1c} (mmol/mol)*	63 (16)	62 (13)	7.9
Donor age (years)	36.2 (13.4)	35.3 (14.0)	7.1
Living donor	5 (6%)	3 (8%)	4.0
Other variables†			
First kidney transplantation	76 (95%)	39 (98%)	11.4
Initial SPK	45 (56%)	20 (50%)	10.2
Male donor	48 (60%)	33 (83%)	43.8
Donor BMI (kg/m ²)	23.7 (4.1)	24.8 (5.1)	22.7
Cold ischaemia time (h)	14.9 (7.1)	15.4 (7.0)	7.3
ABDR mismatches	3.9 (1.4)	3.6 (1.4)	16.0

Data are n (%) or mean (SD). eGFR=estimated glomerular filtration rate. MDRD=modification of diet in renal disease. SPK=simultaneous-pancreas-kidney. ABDR=HLA-A, HLA-B, HLA-DR mismatches. *These variables were considered for matching as time-dependent variables. †These covariables are not present in the causal pathway and do not influence the probability of being treated with islet transplantation and the outcomes.

Table 1: Patient characteristics

two infusions and 16 (34%) received three infusions (appendix pp 19). The median time to complete the whole procedure of islet transplantation was 3.3 months (IQR 1.8–8.6). Three patients in the IAK transplantation group experienced islet primary non-function. In line with the intent to treat study design these patients were not excluded from the analysis. All patients were taking insulin before islet transplantation. After islet transplantation, the probability of insulin requirement was 46.8% at 3 years (95% CI 33.8–61.9), 53.7% at 5 years (40.2–68.5), and 61.2% at 10 years (46.3–76.4; figure 2A). The probability of islet graft exhaustion (ie, c-peptide under 0.3 ng/ml) was 12.8% at 3 years (95% CI 5.9–26.2), 12.8% at 5 years (5.9–26.2), and 21.9% at 10 years (11.8–38.5; figure 2B). Overall, eight patients who had IAK transplantation died with a functioning islet graft, including three patients who died while insulin-independent.

Following the computation of time-dependent propensity scores for the entire population, 40 patients given IAK transplantation were matched with 80 controls at the moment of islet transplantation. Six kidney transplant patients assigned to the control group at the time of matching received an islet transplantation

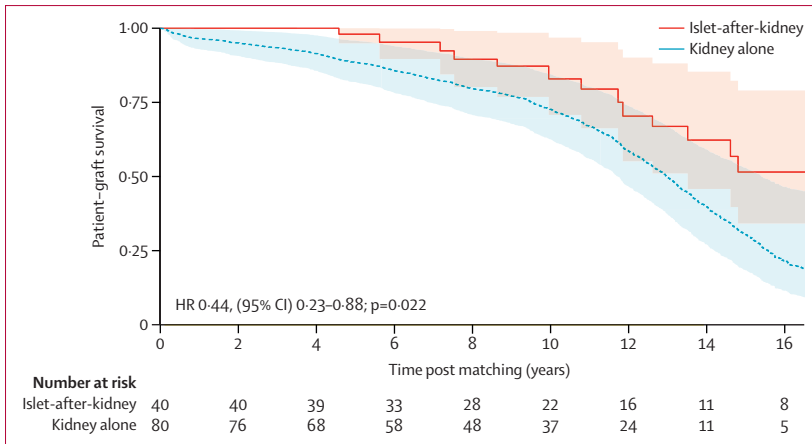


Figure 3: Patient-graft survival in patients with type 1 diabetes treated with islet-after-kidney transplantation or kidney transplantation alone
Representation of bootstrapped Kaplan-Meier survival curves after matching of patients with islet-after-kidney transplantation and patients with kidney transplantation alone (1000 bootstrapped samples). Shaded areas represent 95% CI.

	n/N	10-year survival (95% CI)	Hazard ratio (95% CI)
Patient-graft survival			
Kidney alone	36/80	72.7% (57.4-88.0)	1.00 (reference)
Islet-after-kidney	13/40	82.9% (66.6-99.2)	0.44 (0.23-0.88)
Death-censored graft survival			
Kidney alone	16/80	81.6% (70.2-93.1)	1.00 (reference)
Islet-after-kidney	8/40	85.5% (70.7-100)	0.73 (0.30-1.89)
Patient survival			
Kidney alone	25/80	73.0% (57.4-88.5)	1.00 (reference)
Islet-after-kidney	8/40	90.7% (80.5-100)	0.41 (0.13-0.91)

By design, origin and start times of the survival analysis were identical for each outcome (islet transplantation for islet-after-kidney and the equivalent time of follow-up after kidney transplantation for controls). End time for patient-graft survival was death, return to dialysis, re-transplantation, or end of follow-up. End time for patient survival was death or end of follow-up. End time for death-censored graft survival was death, return to dialysis, re-transplantation, or end of follow-up.

Table 2: Effect of islet-after-kidney transplantation on the risk of death and return to dialysis

subsequently to the matching, with a median time between matching and islet transplantation of 4.6 years (1.8-8.1). One patient in the IAK transplantation group was never involved in the matching process. Baseline characteristics were similar between these groups (table 1).

For the primary outcome, 13 (33%) of 40 patients in the IAK transplantation group returned to dialysis or died, compared with 36 (45%) of 80 patients in the kidney transplantation alone group. The probability of patient-graft survival for IAK transplantation recipients was 98.0% at 5 years (95% CI 94.7-100) and 82.9% at 10 years (66.6-99.2), compared with 88.6% at 5 years (80.6-96.6), and 72.7% at 10 years (57.4-88.0) for kidney transplantation alone recipients (figure 3).

27 (68%) of 40 patients in the IAK transplantation group and 54 (55%) of 80 patients in the kidney transplantation alone group were right-censored at their end of follow-up. There was a significant association between IAK transplantation and overall patient-graft survival (HR 0.44, 95% CI 0.23-0.88; p=0.022, table 2). Given the notable effect of IAK transplantation using this target trial method, we proceeded to investigate its effect on life expectancy with a functional graft. After 15 years, life expectancy with a functional graft for IAK transplantation recipients was 13.2 years (95% CI 12.1-14.0), compared with 11.5 years in patients with kidney transplantation alone (10.2-12.5), demonstrating a significant increase of life expectancy with functional graft of 19.6 months (95% CI 2.3-37.8; figure 3). Ultimately, the number of patients needed to be treated to prevent a single death or return to dialysis was 4.0.

We then analysed secondary outcomes. After matching, eight (20%) of 40 patients in the IAK transplantation group died, compared with 25 (31%) of 80 patients in the kidney transplantation alone group. The main cause of death in both groups was infectious diseases (n=11), followed by cardiovascular diseases (n=8; appendix p 21).

The probability of patient survival for IAK transplantation recipients was 93.1% at 5 years (95% CI 85.1-100) and 90.7% at 10 years (80.5-100), compared with 89.8% at 5 years (82.3-97.3) and 73.0% at 10 years (57.4-88.5) for kidney transplantation alone recipients (appendix p 16). 32 patients (80%) in the IAK transplantation group and 55 patients (69%) in the kidney transplantation alone group were right-censored at their end of follow-up. There was a significant association between IAK transplantation and the probability of death (HR 0.41, 95% CI 0.13-0.91; p=0.042, table 2). At 15 years' follow-up, life expectancy for IAK transplantation recipients was 13.7 years (95% CI 12.5-14.6), compared with 11.9 years for kidney transplantation alone recipients (10.5-13.1), demonstrating a significant increase in life expectancy of 20.1 months (95% CI 2.1-43.4; appendix p 16). The number of patients needed to be treated to prevent a single death was 3.2.

For death-censored graft survival, after matching, eight (20%) of 40 patients returned to dialysis or received another kidney transplant, compared with 16 (20%) of 80 patients in the kidney transplantation alone group. The probability of death-censored graft survival was 98.0% at 5 years (95% CI 94.7-100) and 85.5% at 10 years (70.7-100) in IAK transplantation recipients, compared with 89.8% at 5 years (82.3-97.3), and 81.6% at 10 years (70.2-93.1) in kidney transplantation alone recipients (appendix p 17). 27 (68%) patients in the IAK transplantation group and 36 (45%) in the kidney transplantation alone group were right-censored at their end of follow-up. Five patients (13%) in the IAK transplantation group and 19 patients (24%) in the kidney transplantation alone group were left-censored due to death.

After matching, we observed an estimated 27 percentage point reduction of the risk of returning to dialysis in the

IAK transplantation group (HR 0.73, 95% CI 0.30–1.89; $p=0.36$, $S=1.46$ bits), a result which was inconclusive, suggesting the need for further larger studies.

Finally, we evaluated the effect of IAK transplantation on metabolic control compared with kidney transplantation alone. At the time of matching HbA_{1c} in kidney transplantation alone and IAK transplantation recipients were similar (IAK transplantation 7.8% [62 mmol/mol], SD 1.3% [14 mmol/mol] vs kidney transplantation alone 7.9% [63 mmol/mol], 1.5% [16 mmol/mol]). HbA_{1c} was analysed at each timepoint after the time of matching, based on the 1000 bootstrap datasets. IAK transplantation was associated with significantly lower concentrations of HbA_{1c} compared with kidney transplantation alone at all timepoints from 6 months (IAK transplantation 6.4% [46 mmol/mol], SD 1.1% [12 mmol/mol] vs kidney transplantation alone 8.2% [66 mmol/mol], 1.8% [20 mmol/mol]; $p<0.0001$) to 5 years (IAK transplantation 6.5% [48 mmol/mol], 0.9% [9 mmol/mol] vs kidney transplantation alone 7.9% [63 mmol/mol], 1.7% [18 mmol/mol]; $p<0.0001$, figure 4).

Discussion

The KAIK nationwide target trial showed a significant association between islet transplantation and a reduced risk of death or return to dialysis in kidney transplant recipients with type 1 diabetes. This resulted in a significant increase in both life expectancy with a functioning graft and the overall life expectancy in patients treated with IAK transplantation.

β -cell replacement with islet transplantation emerges as an efficacious strategy for optimising metabolic control in type 1 diabetes,¹ resulting in a significant improvement of quality of life⁵ and a possible positive economic impact.¹⁹ However, long-term data evaluating hard clinical endpoints after islet transplantation are scarce, especially in a vulnerable population such as patients with type 1 diabetes with end stage renal disease.

In a retrospective cohort analysis encompassing 34 kidney transplant recipients with type 1 diabetes who underwent islet transplantation, Fiorina and colleagues uncovered an association between the extended function of transplanted islets and enhanced survival in comparison to those whose islet function declined within a year post-transplantation.⁸ In subsequent work, these authors compared the outcomes of islet–kidney transplantation with pancreas–kidney transplantation and kidney transplantation alone, suggesting a benefit of islet or pancreas transplantation on kidney graft survival compared with kidney transplantation alone.⁹ Although these studies held substantial interest, it should be noted that they were conducted during the late 1990s, with significant differences at baseline between groups. Other investigations have scrutinised the benefits of islet transplantation in the context of islet–kidney recipients, often without control groups. These studies suggested that islet transplantation led to improved glycaemic control

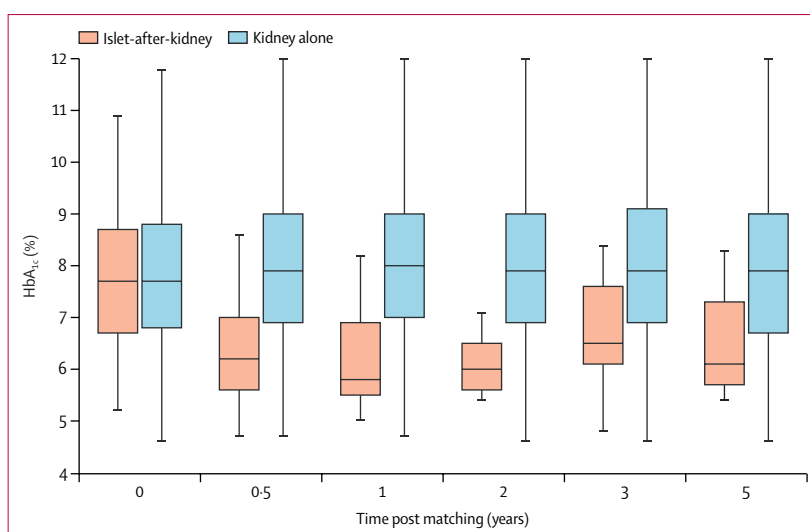


Figure 4: HbA_{1c} after matching in patients with type 1 diabetes treated with islet-after-kidney transplantation or kidney transplantation alone

Results were obtained on the 1000 bootstrap samples to mitigate any bias that might arise from a single matched sample. Boxes show median, 25th and 75th percentiles. Whiskers indicate 1.5 IQR.

post-transplantation,²⁰ even in the contemporary era of continuous glucose monitoring and closed loop insulin pumps.³ Islet transplantation did not exhibit a heightened risk of sensitisation^{21,22} and the risk of adverse events was moderate.^{3,20} Furthermore, various studies have hinted at an enhancement in quality of life following islet transplantation.^{3,20} We observed a substantial reduction in HbA_{1c} ($\geq 1.5\%$ during at least 5 years) in the treatment group. The relation between metabolic and survival results observed in our study is consistent with the results of the Diabetes Control and Complications Trial (DCCT)²³ and its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC).²⁴ In these, intensive diabetes therapy resulted in 1.6% reduction of HbA_{1c} over an average of 6.5 years. The benefits of this improved glycaemic control persisted even after the trial ended, despite both treatment groups achieving similar blood glucose levels during the EDIC follow-up, resulting in a durable 50% reduction of the risk of impaired renal function²⁵ and a 33 percent reduction of all-cause mortality after 27 years.²⁶ Of note, in our study, causes of death probably related to metabolic control (cardiovascular disease, infection, or hypoglycaemia) were more represented in the kidney transplantation alone group than in the IAK transplantation group.

Our findings should be interpreted considering certain limitations. Target trials represent one of the best alternatives when randomised controlled trials are not feasible. However, unlike randomised trials, in which multiple outcomes can be assessed post-randomisation, the outcome-focused variable selection process in propensity score analyses limits evaluation to only the predetermined outcome, warranting cautious interpretation of subgroup analyses and any secondary results. Some residual

confounding might therefore persist. Firstly, the construction of direct acyclic graphs to select covariates of interest for matching is inherently limited by the quality and comprehensiveness of the background information. One can therefore not exclude that underlying confounders were inadvertently omitted. Secondly, islet transplantation became standard care in France in 2021, thus all IAK transplantation participants received islet transplantation in the context of clinical trials or compassionate use, potentially resulting in a stricter follow-up. Thirdly, half of the participants in the IAK transplantation group received mTOR inhibitors, by contrast with the kidney transplantation alone group in which all patients received mycophenolate mofetil. However, available data do not substantiate any association between mTOR inhibitors and prolonged life expectancy after kidney transplantation.^{27,28} Several aspects might also limit the generalisability of our results that were obtained from a nationwide cohort. Likewise, half of the kidney recipients in the study initially received a simultaneous pancreas transplantation, a procedure known to be proposed only to a selected population among patients with type 1 diabetes and end stage renal failure. This could consequently limit the generalisability of our findings to other populations of kidney recipients such as elderly or more fragile recipients. Of note, our study yields islet graft survival and insulin independence rates similar to other cohorts.^{29,30} Finally, the landscape of insulin treatment has regularly evolved in the past 20 years driven by technological advancements. For example, insulin pump and continuous glucose monitoring qualified for reimbursement in France in 2000 and 2017 respectively. Therefore, all the study participants with or without islet transplantation, had equal access to best medical care according to French guidelines in force during the study period. Consequently, our results should be validated again in the future to compare islet transplantation with these more advanced therapies in diabetes management. Finally, the sample size of our study was determined by the total number of kidney transplant patients with type 1 diabetes who were eligible to IAK transplantation in France during the study period. However, regarding the specific risk reduction of returning to dialysis in the IAK transplantation group, the width of 95% CI of the point estimate calls for further studies with larger sample size to conclude.

In conclusion, we showed that in patients with type 1 diabetes and a kidney transplant, islet transplantation was associated with a significantly prolonged life expectancy with a functioning kidney graft. Taken together with existing literature, these results justify the implementation of β -cell replacement in addition to kidney transplantation as standard care in patients with type 1 diabetes and end stage renal failure.

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Contributors

MM and RL had access to the raw data and verified the data. Study conceptualisation: MM, RL, YF, LB, LE, MC, AH, JK-C, TB, M-CV, MH, FP. Data acquisition: MM, FB, GB, CA, SC, LK, MLQ, OV, DA, MB, AB-S, LF, PM, SL. Statistical analysis: RL, YF. Manuscript drafting: MM, RL, YF, MC, MH, FP. Critical revision for important intellectual content: all authors. Manuscript approval: all authors. MM and FP were responsible for the decision to submit for publication.

Declaration of interests

MM, RL, YF, FB, GB, CA, LK, MLQ, DA, MB, AB-S, LF, PM, SL, LB, LE, MC, AH, JK-C, TB, M-CV, MH, and FP declare no competing interests. SC declares support for attending meetings or travel from Astra Zeneca, Alexion, Sanofi, and Pierre Fabre and participation on a data safety monitoring board or advisory board from Astra Zeneca, Alexion, Chiesi, Pierre Fabre, Pfizer, and Samsung Bioepis. OV declares payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Sanofi-Aventis, Eli-Lilly, and Novo-Nordisk and support for attending meetings or travel from Sanofi-Aventis.

Data sharing

The datasets generated during or analysed during the current study are available from the corresponding authors on reasonable request.

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