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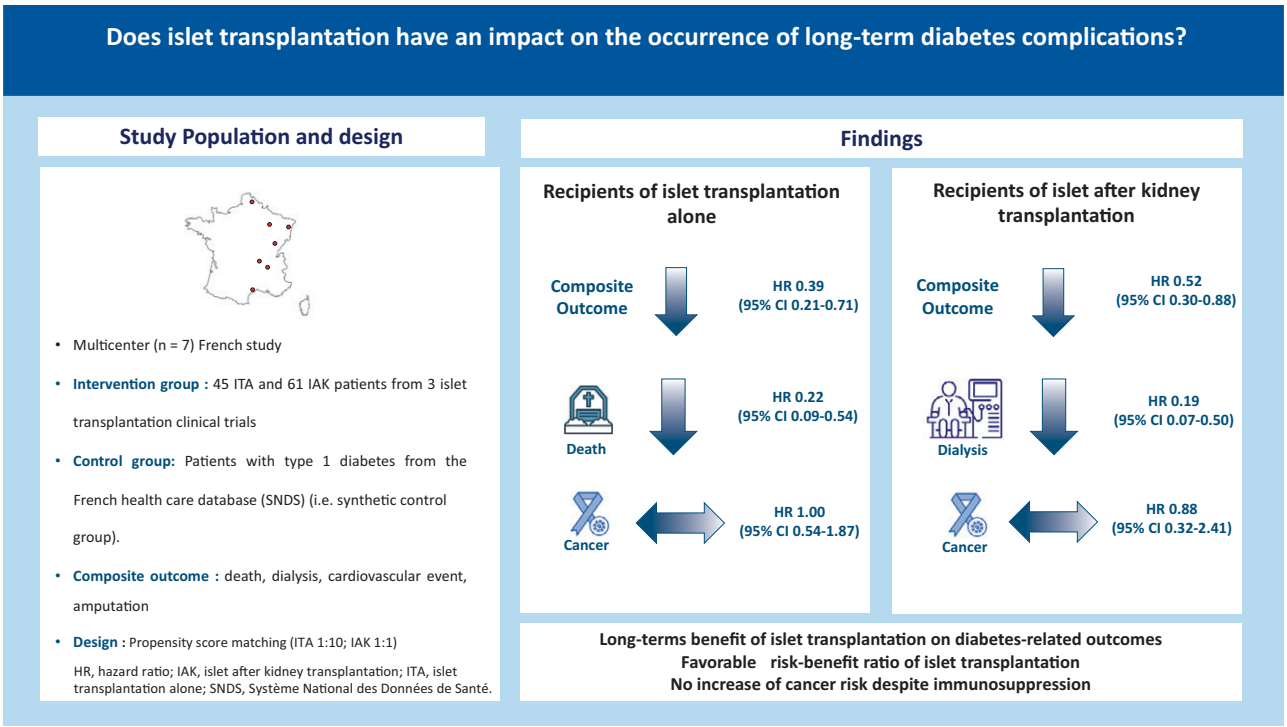

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Islet transplantation (IT) is a minimally invasive technique used to improve glycemic control and quality of life, prevent severe hypoglycemia, and achieve insulin independence, but comparative information with patients not receiving IT is currently lacking.
- **What is the specific question we wanted to answer?**
  What are the long-term benefits and risks of IT on diabetes-related complications and cancers induced by immunosuppressive treatment compared with patients with type 1 diabetes treated with insulin?
- **What did we find?**
  IT is associated with a lower risk of diabetes complications, mainly mortality reduction in IT recipients and return to dialysis in IT after kidney transplant recipients, without differences in cancer risk.
- **What are the implications of our findings?**
  IT offers long-term benefits for type 1 diabetes complications, with a favorable risk-benefit ratio.

Impact of Islet Transplantation on Diabetes Complications and Mortality in Patients Living With Type 1 Diabetes

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OBJECTIVE

This study aimed to evaluate the impact of islet transplantation (IT) on diabetes complications, death, and cancer incidence.

RESEARCH DESIGN AND METHODS

This retrospective, multicenter, cohort study included patients from three IT clinical trials (intervention group) and from the French health insurance claims database Système National des Données de Santé (SNDS) (control group). Two cohorts of IT recipients were analyzed: IT recipients after kidney transplantation (IAK) and IT recipients alone (ITA). They were matched with patients living with type 1 diabetes (T1D) from the SNDS using a propensity score. The primary outcome was a composite criterion including death, dialysis, amputation, nonfatal stroke, nonfatal myocardial infarction, and transient ischemic attack. The secondary outcome was cancer. Hazard ratio (HRs) and *P* values were obtained using Cox proportional hazards analysis and log-rank test, respectively.

RESULTS

The study included 61 ITA recipients matched to 610 T1D control patients and 45 IAK recipients matched to 45 T1D control patients over a median follow-up period >10 years. Compared with T1D control patients, ITA and IAK recipients had a lower composite outcome risk (HR 0.39 [95% CI 0.21–0.71; *P* = 0.002] and 0.52 [0.30–0.88; *P* = 0.014], respectively) that seemed driven by reduced mortality (0.22 [0.09–0.54]; *P* < 0.001) for ITA and reduced dialysis (0.19 [0.07–0.50]; *P* < 0.001) for IAK. Both groups showed no significant changes in cancer risk.

CONCLUSIONS

This study suggests long-term benefits of IT on diabetes-related outcomes. Furthermore, despite the use of immunosuppressive drugs following IT, we observed no significant increase in the risk of cancer. Altogether, these findings highlight a favorable risk-benefit ratio of IT in treating patients with unstable T1D.

Despite intensive insulin therapy, people living with type 1 diabetes (T1D) still have a high risk of microvascular and macrovascular complications (1,2). Islet transplantation (IT) is a minimally invasive technique used to improve glycemic control, prevent severe hypoglycemia, improve quality of life, and achieve insulin independence, with the rate of insulin independence varying based on center

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**A complete list of the members of GRAGIL Network is provided in the supplementary material online.*

experience and transplantation strategy (3–5). Based on these results, IT is now considered a therapeutic option for people living with unstable T1D (islet transplantation alone [ITA]) and people living with T1D and functional kidney graft (islet after kidney transplantation [IAK]), especially in European countries (6).

If IT metabolic outcomes are well described, as well as the long-term impacts of IT on recipients' mortality and diabetes complications or return to dialysis, comparative information with patients not undergoing IT is poorly described. Indeed, when considering mortality among IT recipients, data from the Collaborative Islet Transplant Registry (CITR) indicated a 5-year survival probability of 97.7% (7). The Groupe Rhin Rhône Alpes Genève pour la transplantation d'îlots de Langerhans (GRAGIL) group observed a 10-year survival probability of 86.4% (5), while the Edmonton group reported a 20-year survival probability of 75% (8). Recently, a study conducted in Miami, Florida, involving 49 IT recipients demonstrated that IT does not increase mortality related to long-term immunosuppressant use compared with patients with type 1 diabetes (T1D) not transplanted (9). However, this conclusion was based on epidemiological data from national diabetes registries spanning different periods without matched patient data. The rate of cancer incidence was 13.6% at 10 years (5) and remained stable at 20 years (8), with a predominance of skin cancers (33%).

Regarding kidney function, the most recent studies (10,11) indicated that following IAK, an initial decline in glomerular filtration rate (GFR) was observed (-10 to -20 mL/min). However, kidney function subsequently recovered and, in the best cases, either continued to improve, remained stable, or showed a decline similar to that seen in healthy individuals (-1 to -2 mL/min/year). Finally, for the benefits of IAK, a few comparative studies are available. In a cohort followed for 3 years, Fiorina and colleagues (12,13) demonstrated an improvement in cardiovascular function and kidney graft survival in the IAK group compared with the kidney-transplanted group without IT. Another recent study focusing on IAK recipients showed that IAK improves patient-graft survival based on a composite end point that associated graft failure with return to dialysis, kidney retransplantation, and death compared with patients with kidney graft and T1D but without IT (14).

Therefore, further investigation is needed to determine the long-term benefits of IT based on overall diabetes-related complications. The objective of this study was to evaluate the impact of IT on diabetes complications such as death, dialysis, amputation, myocardial infarction, stroke, transient ischemic attack, return to dialysis for IAK, and immunosuppressive treatment complications such as cancer.

RESEARCH DESIGN AND METHODS

This multicenter cohort study complied with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies (15). The protocol was published online before the study started (Open Science Framework registry, https://osf.io/c25pv/).

Data Source

The study was conducted from the individualized data of patients from databases built following the previously published GRAGIL trial and Trial Comparing Metabolic Efficiency of Islet Graft to Intensive Insulin Therapy for Type 1 Diabetes's Treatment (TRIMECO) (ClinicalTrials.gov identifiers: NCT00639600, NCT00321256, and NCT01148680) (16–18) and data extracted from the French health insurance claims database Système National des Données de Santé (SNDS). SNDS covers the entire population of France (67 million residents), of which 87% are covered by the national health insurance general scheme. Each person is identified by a unique, anonymous number. Since 2006, SNDS has recorded information on all outpatient care (including drugs, imaging, and laboratory tests) and inpatient care (including medical diagnoses, ICD-10 codes, and procedures performed as coded according to the Common Classification of Medical Procedures). The health expenses for patients with long-term disease, such as cancer, diabetes, and their related complications, are fully reimbursed, and their diagnoses are registered according to ICD-10 coding. SNDS has been extensively used and described, and all codes used for characteristic identification have been previously described (19–21).

Study Population

Our experimental cohort was composed of two subgroups: a group of all clinical trial patients with a kidney transplant before IT (IAK cohort) and a group of all other clinical trial patients (ITA cohort). The initial sample for the experimental group (i.e., clinical trial patients) consisted of all IT recipients in the GRAGIL trial, TRIMECO with its extension, and Swiss IT recipients (estimated n = 150). However, due to a regulatory issue, we were not able to obtain data from the Swiss IT recipients, so the final experimental cohort was composed of 106 IT recipients with 45 IAK and 61 ITA recipients transplanted between 1999 and 2016.

Our nonexposed cohort was composed of a synthetic control group identified from the SNDS. First, we identified every patient with T1D with at least 5 years of insulin use before inclusion, no reimbursement for oral glucose-lowering drugs, and a follow-up of up to 10 years. As the SNDS includes data from 1 January 2006 through 31 December 2022, we included patients between 1 January 2011 and 31 December 2012 to ensure a minimum diabetes duration and follow-up. Second, we selected patients $>$18 years old at the inclusion date. Third, we divided our cohort of patients with T1D into two distinct cohorts: *1*) patients with T1D without a kidney transplant and *2*) patients with T1D with a kidney transplant. Fourth, we excluded patients with fewer than two hospitalizations for diabetes or diabetes complications in the year preceding inclusion (i.e., proxy for diabetes severity) for the group without kidney transplant. We excluded patients with $<$3 years between kidney transplant and the inclusion date for the group with kidney transplant. Fifth, to ensure that patients in our control group were not in the experimental group, we excluded every patient with the same sex, birth month, birth year, and death status (dead or alive) on 31 December 2022. A flow diagram of the SNDS patient selection and timeline for the selection of the control group are presented in Supplementary Figs. 1 and 2.

Finally, for both cohorts, each patient included in the experimental group was

matched using greedy matching on propensity score with a caliper width of 0.2 SDs of the logit at a ratio of up to 1:10 (i.e., 1 experimental group patient matched to 10 synthetic control group patients) for the ITA cohort and 1:1 for the IAK cohort. We constructed the propensity score with conditional logistic regression stratified by an IT set to predict the probability of receiving IT compared with no IT using known and identifiable risk factors for diabetes severity. The covariates used for the propensity score were sex, age, history (in the 5 years prior to the index date) of dialysis, amputation, stroke, transient ischemic attack, and myocardial infarction. Codes used for covariate identification are presented in Supplementary Table 1.

Outcome Definitions

The primary outcome was defined as the first occurrence of a composite criterion composed of various events: death, dialysis, amputation, nonfatal stroke, nonfatal myocardial infarction, or transient ischemic attack. The secondary outcome was defined as the first occurrence of a cancer: breast cancer, colorectal cancer, pulmonary cancer, prostate cancer, or other classified cancer (e.g., skin cancer). Codes used for event identification are presented in Supplementary Table 2.

Ethical Obligation

All patients had previously given their consent for the retrospective use of their hospital care data. This study obtained ethical approval from a local ethics committee (CERGA-Avis-2013-15). For patients included in the synthetic control group from the SNDS, no informed consent was required because only anonymous data were used under the French Data Protection Supervisory Authority agreement.

Statistical Analyses

We calculated descriptive summary characteristics for the study population by exposure status for quantitative parameters (mean and SD or median and 25th to 75th percentiles) and qualitative parameters (number and percentage of patients), and normality was graphically assessed. We used standardized mean difference (SMD) instead of the *P* value to assess whether our matching was efficient because of the large number of patients. An absolute SMD $\leq$10% indicated a negligible difference in potential confounders and balanced matched cohorts (22). We compared the occurrence of events between groups using a survival analysis (log-rank test). As a sensitivity analysis, we conducted a Cox proportional hazards analysis in both propensity score–matched cohorts (Supplementary Table 3) to assess the robustness of the method. We estimated the hazard ratio (HR) and 95% CI for each end point in individuals with IT. Patients with missing data on sociodemographic variables were excluded. All statistical analyses were performed using SAS Enterprise Guide version 7.13 or higher (SAS Institute, Cary, NC), R version 4.2.1 or higher (R Foundation for Statistical Computing), and PASS version 15 (NCSS, LLC, Kaysville, UT).

Data and Resource Availability

According to data protection and French regulations, the authors cannot publicly release the data from the SNDS. However, any person or organization (public or private, for-profit, or nonprofit) can access anonymized SNDS data to perform a study, research, or an evaluation of public interest upon authorization from the French Data Protection Office (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://documentation-snds.health-data-hub.fr/introduction/03-acces-snds.html).

RESULTS

Description of Population and Matching Parameters

The experimental group was composed of two distinct populations: a first population of 61 ITA recipients with a median duration of T1D of 31.6 (25th–75th percentile 24.5–39.3) years and a median follow-up after IT of 10.4 (8.7–13.6) years and a second population of 45 IAK recipients with a median duration of T1D of 32.6 (26.9–40.9) years, a median follow-up after IT of 13.4 (8.2–17.4) years, and a median delay between kidney and IT of 3.9 (2.6–6.4) years (kidney transplantation occurred between 1990 and 2011). Detailed anthropometric data and preexisting T1D-related complications (before IT for the experimental group or before inclusion for the control group) are compiled in Table 1. Overall, 61 ITA recipients were matched on propensity score to 610 control patients from the synthetic group, achieving a satisfactory level of global matching (absolute SMD $<$10%) except for stroke history (SMD $-$11.4%) in disfavor of the control group (i.e., there were more patients with a history of stroke in the control group). Forty-five IAK recipients were matched on propensity score to 45 control patients, with a median delay between kidney transplantation and inclusion of 3.72 (3.00–4.51) years and a lower matching quality compared with ITA (three absolute SMDs $>$10% for transient ischemic attack, age, and myocardial infarction [10.8%, 30.2%, and 26.2%, respectively]) in disfavor of the IAK group (i.e., there were more patients with the presence of the characteristic in the intervention group). SMD distributions at baseline and postmatching for the two groups are presented in Supplementary Fig. 3*A* and *B*.

Positive Impact of ITA on Mortality Without a Significant Increase in Cancer Risk

ITA recipients exhibited a significantly lower occurrence of the primary outcome compared with control patients without IT (HR 0.39 [95% CI 0.21–0.71]; $P = 0.002$) (Table 2 and Fig. 1*A*). This difference was predominantly driven by a significant reduction in mortality among ITA recipients (0.22 [0.09–0.54]; $P < 0.001$) (Fig. 2). There was no statistical difference regarding macrovascular complications, including stroke, myocardial infarction, transient ischemic attack, or amputation ($P > 0.05$) (Table 2), or in cancer outcome between the two groups (1.00 [0.54–1.87]; $P = 1$) (Fig. 2). Kaplan-Meier survival curves for all subcriteria in the ITA group are presented in Supplementary Figs. 4–13.

Positive Impact of IAK on Dialysis Occurrence After IT Without a Significant Increase in Cancer Risk

IAK recipients exhibited a significantly lower occurrence of the primary outcome compared with control patients with kidney transplant alone (HR 0.52 [95% CI 0.30–0.88]; $P = 0.014$) (Table 2 and Fig. 1*B*). This difference was predominantly driven by significantly less dialysis among IAK recipients (0.19 [0.07–0.50]; $P < 0.001$) (Fig. 2). IAK recipients statistically exhibited a higher occurrence of myocardial infarction compared with patients with kidney transplant alone (4.24 [1.18–15.2]; $P = 0.016$) (Table 2). There

Table 1—Baseline and postmatching characteristics of patients

	Baseline (n = 6,310)			Postmatching (n = 671)		
Characteristic	Experimental group	Synthetic control group	SMD (%)	Experimental group	Synthetic control group	SMD (%)
Patients with ITA, *n*	61	6,249		61	610	
Male sex	31 (50.8)	3,480 (55.7)	9.7	31 (50.8)	296 (48.5)	−4.6
Age, years (mean ± SD)	50.1 ± 10.5	42.5 ± 11.4	72.0	50.1 ± 10.5	49.2 ± 9.2	8.9
Dialysis	0 (0.00)	461 (7.37)	28.4	0 (0.00)	0 (0.00)	0.0
Amputation	1 (1.64)	330 (5.28)	28.7	1 (1.64)	10 (1.64)	0.0
Stroke	3 (4.92)	123 (1.97)	13.6	3 (4.92)	45 (7.38)	−11.4
Transient ischemic attack	0 (0.00)	44 (0.70)	8.5	0 (0.00)	0 (0.00)	0.0
Myocardial infarction	6 (9.84)	137 (2.19)	25.7	6 (9.84)	67 (11.0)	−3.9
	Baseline (n = 244)			Postmatching (n = 90)		
Patients with IAK, *n*	45	199		45	45	
Male	28 (62.2)	107 (53.8)	−17.2	28 (62.2)	26 (57.8)	−9.1
Age, years (mean ± SD)	45.2 ± 9.0	49.8 ± 8.9	−51.6	45.2 ± 9.0	42.4 ± 11.2	30.2
Dialysis	25 (55.6)	171 (85.9)	−61.1	25 (55.6)	25 (55.6)	0.0
Amputation	5 (11.1)	20 (10.1)	3.4	5 (11.1)	6 (13.3)	−7.1
Stroke	3 (6.67)	3 (1.50)	20.7	3 (6.67)	3 (6.67)	0.0
Transient ischemic attack	2 (4.44)	1 (0.50)	19.1	2 (4.44)	1 (2.22)	10.8
Myocardial infarction	6 (13.3)	5 (2.51)	31.8	6 (13.3)	2 (4.44)	26.2

Data are *n* (%) unless otherwise indicated.

was no statistical difference in cancer outcome between the two groups (0.88 [0.32–2.41]; P = 0.80) (Fig. 2). Kaplan-Meier survival curves for all subcriteria of the IAK group are presented in Supplementary Figs. 14–23.

CONCLUSIONS

The findings of this study shed light on the long-term impact of ITA and IAK for people living with unstable T1D and those with T1D and kidney transplant and provide comprehensive insights into the long-term benefits (>10 years) and potential risks associated with ITA and IAK. It is important to highlight that these positive results for IT were achieved without long-term insulin independence. Indeed, <5% of patients in the GRAGIL trials (5) remained insulin independent 10 years after islet infusion (although 50% had a functional graft), while 59% of patients in TRIMECO (18) remained insulin independent 1 year after islet infusion (with 85% having a functional graft).

Regarding the population of patients undergoing ITA, numerous studies have demonstrated improvements in metabolic parameters (reduction in glycemic variability, decrease in HbA_{1c} levels), prevention of severe hypoglycemia, and enhancement of quality of life (3,4,16–18). Unfortunately, there are limited comparative data on the impact of ITA on serious diabetes-related complications such as death, cardiovascular complications, amputation, and dialysis. Only Lemos et al. (9) reported a trend of no increased risk with ITA compared with historical data from the Pittsburgh Epidemiology of Diabetes Complications and the Allegheny County T1D registry cohort. One of the notable observations from our study was the significant reduction in the composite end point frequency among patients who underwent ITA compared with those who did not. Although the benefit on the composite outcome seemed to be driven by the reduction of mortality, this interpretation should be made with caution due to the limited number of events. Furthermore, our study suggests that there is no significant difference on cardiovascular events (myocardial infarction, stroke, transient ischemic attack) and lower-limb amputation associated with IT in ITA population.

Nakamura et al. (23) reported a cancer incidence of 43% (3 of 7) among IT recipients compared with 4% (1 of 26) in patients treated with multiple daily injections of insulin over the same period. The higher cancer prevalence observed in this study (vs. 13% previously published [5,8] and >20% observed in our cohort) can likely be attributed to the small sample size. Moreover, the increased risk reported in this study was observed in nonmatched patients who did not share comparable characteristics. Matching was performed based on age, C-peptide negativity, and baseline creatinine levels but not on the presence of unstable T1D. In our cohort, the absence of a significant increase in the risk of cancer following ITA is a noteworthy finding, considering the use of immunosuppressive regimens previously described (induction with thymoglobulin or interleukin-2 inhibitor and maintenance with calcineurin inhibitor, mammalian target of rapamycin inhibitor, or mycophenolate acid) (16–18). While immunosuppressive treatment is known to carry oncogenic risks, the current study provides reassurance regarding the safety profile of ITA in this regard. It should be noted that the median follow-up period of this cohort of >10 years may not be sufficient to detect certain cancers that emerge years after transplantation but remains compatible with the delay in cancer development reported in the literature. The literature indicates an increased risk of cancer (mostly liver, pancreatic, colorectal, endometrial, and kidney) in mostly patients with type 2 diabetes but also in patients with T1D compared with individuals without diabetes (24,25). Taken together, these studies could suggest that the risk of cancer in patients with diabetes is related to glycemic control (as it is present regardless the types of diabetes). Based on these data, we hypothesize that the better glycemic control offered by ITA (already well demonstrated for patients included in our

Table 2—Outcomes for the ITA and IAK groups

	ITA								IAK							
	Experimental group (*n* = 61)			Synthetic control group (*n* = 610)			Statistical test		Experimental group (*n* = 45)			Synthetic control group (*n* = 45)			Statistical test	
	Events *n* (%)	Person-years, *n*	Incidence rate*	Events, *n* (%)	Person-years, *n*	Incidence rate*	Log-rank *P*	HR† (95% CI)	Events *n* (%)	Person-years, *n*	Incidence rate*	Events, *n* (%)	Person-years, *n*	Incidence rate*	Log-rank *P*	HR† (95% CI)
Outcome																
Composite	15 (24.6)	652	2.30 (1.29–3.60)	265 (42.1)	5,532	4.79 (4.23–5.38)	0.002	0.39 (0.21–0.71)	32 (71.1)	464	6.89 (4.71–9.48)	33 (73.3)	284	11.60 (7.99–15.88)	0.014	0.52 (0.30–0.88)
Death	8 (13.1)	692	1.16 (0.50–2.09)	208 (34.1)	5,843	3.56 (3.09–4.06)	< 0.001	0.22 (0.09–0.54)	16 (35.6)	592	2.70 (1.54–4.18)	17 (37.8)	440	3.86 (2.25–5.90)	0.50	0.78 (0.38–1.61)
Dialysis	7 (11.5)	664	1.05 (0.42–1.97)	53 (8.69)	5,660	0.94 (0.70–1.20)	0.92	1.05 (0.45–2.44)	8 (17.8)	531	1.51 (0.65–2.71)	21 (46.7)	314	6.70 (4.14–9.85)	< 0.001	0.19 (0.07–0.50)
Stroke	4 (6.56)	682	0.59 (0.16–1.29)	39 (6.39)	5,697	0.68 (0.49–0.92)	0.58	0.72 (0.22–2.33)	4 (8.89)	584	0.68 (0.19–1.50)	3 (6.67)	411	0.73 (0.15–1.76)	0.74	1.29 (0.29–5.78)
Myocardial infarction	5 (8.20)	671	0.75 (0.24–1.53)	26 (4.26)	5,763	0.45 (0.29–0.64)	0.46	1.49 (0.52–4.27)	15 (33.3)	475	3.16 (1.77–4.95)	3 (6.67)	428	0.70 (0.14–1.69)	0.016	4.24 (1.18–15.2)
Transient ischemic attack	0 (0.00)	692	—	7 (1.15)	5,805	0.12 (0.05–0.22)	0.38	—	1 (2.22)	577	0.17 (0.00–0.64)	0 (0.00)	440	—	0.31	—
Amputation	0 (0.00)	692	—	33 (5.41)	5,718	0.58 (0.40–0.79)	0.056	—	3 (6.67)	573	0.52 (0.11–1.26)	8 (17.8)	400	2.00 (0.86–3.61)	0.10	0.35 (0.09–1.32)
Cancers																
Any	13 (21.3)	629	2.07 (1.10–3.33)	103 (16.9)	5,451	1.89 (1.54–2.27)	1	1.00 (0.54–1.87)	10 (22.2)	534	1.87 (0.90–3.20)	8 (17.8)	415	1.93 (0.83–3.47)	0.80	0.88 (0.32–2.41)
Breast	2 (3.28)	680	0.29 (0.04–0.82)	13 (2.13)	5,771	0.23 (0.12–0.36)	0.58	1.51 (0.34–6.72)	1 (2.22)	590	0.17 (0.00–0.63)	1 (2.22)	431	0.23 (0.01–0.86)	0.32	—
Colorectal	0 (0.00)	692	—	7 (1.15)	5,805	0.12 (0.05–0.22)	0.39	—	1 (2.22)	592	0.17 (0.00–0.62)	0 (0.00)	440	—	1	—
Pulmonary	0 (0.00)	692	—	20 (3.28)	5,814	0.34 (0.21–0.51)	0.15	—	0 (0.00)	592	—	2 (4.44)	440	0.45 (0.06–1.27)	0.16	—
Prostate	1 (1.64)	689	0.15 (0.00–0.54)	9 (1.48)	5,778	0.16 (0.07–0.27)	0.99	1.01 (0.13–7.98)	1 (2.22)	588	0.17 (0.00–0.63)	1 (2.22)	434	0.23 (0.01–0.85)	0.32	—
Other	11 (18.0)	643	1.71 (0.85–2.86)	71 (11.6)	5,603	1.27 (0.99–1.58)	0.63	1.18 (0.59–2.37)	7 (15.6)	541	1.29 (0.52–2.41)	5 (11.1)	430	1.16 (0.38–2.38)	0.50	1.48 (0.47–4.68)

*Per 100 persons per year (95% CI). †Obtained by Cox proportional hazards analysis. IAK, islet after kidney; ITA, islet transplantation alone; Testlog-rank, log-rank statistical analysis.

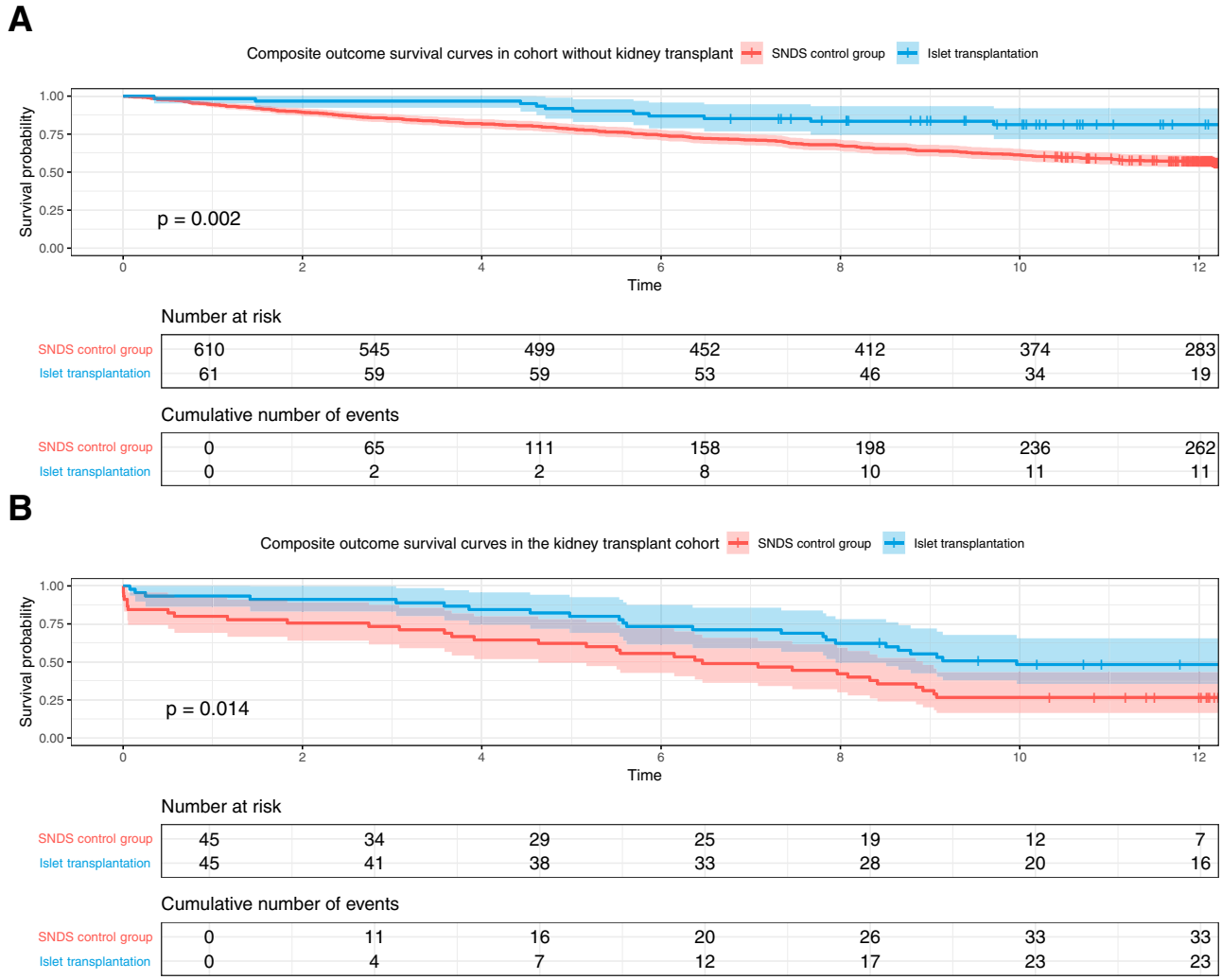

Figure 1—Kaplan-Meier survival curves of the primary composite outcome in the ITA (*A*) and IAK (*B*) groups. Time is given in years.

study [16–18]) may counterbalance the oncogenic risk associated with immunosuppressive treatment used after IT and provide similar oncogenic risk as patients with poorly controlled T1D.

In our study, we observed a significant reduction in the composite end point incidence rate among patients who underwent IAK compared with those with kidney transplant alone. This reduction suggests the potential of IAK to improve long-term outcomes and seems particularly driven by the reduced risk of dialysis (81%). This benefit of IAK on dialysis risk could also be linked to the eligibility criteria for IAK (GFR >50 mL/min) in the experimental group. However, our results are consistent with those of other studies (4,26–28). Several teams have demonstrated stabilization of kidney function at 5 and 10 years after IAK (4,26–28), a positive impact of IT on kidney graft survival (13). Recently, Maanaoui et al. (29) showed a positive impact of IAK on a composite primary end point for patient-graft survival (graft failure with return to dialysis, kidney retransplantation, or death) in 40 IAK recipients with T1D matched on biological and clinical parameters with 80 patients with T1D with kidney transplantation alone. Altogether, these data demonstrate the positive impact of IT of kidney graft function.

Although patients with T1D and kidney transplant received a new immunosuppressive induction at the time of IT, which could increase their oncogenic risk, our study suggests an absence of oncogenic risk in IAK recipients compared with patients with T1D solely transplanted with a kidney. Previous data (30,31) have suggested that the decline in kidney function increases the risk of cancer. IAK is now well known to preserve kidney graft function in selected patients (4,26–28). The absence of oncogenic risk could be linked both to the improvement of glycemic control and the preservation of the kidney graft following IT. However, the data from our study suggest an increased risk of myocardial infarction in the IAK population. This finding contradicts several studies that have demonstrated improvements in cardiovascular function (12) and intima-media thickness (32) and a decrease in coronary calcifications (33). The poorer quality matching of patients between the IAK and control groups, due to a smaller sample size for matching, was done in disfavor of the IAK group for two criteria, age and history of myocardial infarction, which are known risk factors for myocardial infarction (34). This mismatching of patients may therefore contribute to a statistically significant but clinically unverified signal.

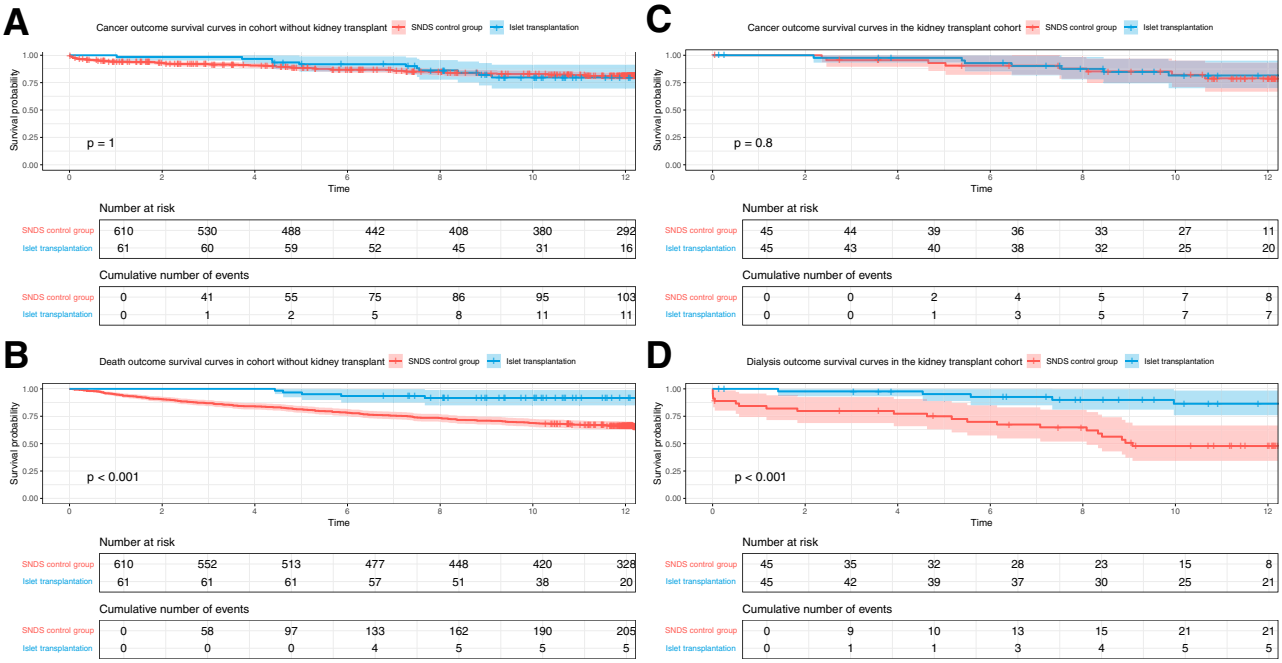

Figure 2—Kaplan-Meier survival curves of the secondary cancer (*A*) and death (*B*) outcomes in the ITA group and the secondary cancer (*C*) and dialysis (*D*) outcomes in the IAK group. Time is given in years.

Nonetheless, special attention should be paid to the evolution of cardiovascular complications for this population of patients.

Automated insulin delivery (AID) therapy is now standard of care for patients living with T1D. One study assessed the effectiveness and safety of a closed-loop hybrid system (Diabeloop Generation 1, DBLG1) in seven patients with highly unstable T1D and potential candidates for IT and showed glycemic stabilization benefits (35). Another study demonstrated the utility of a closed-loop system (Control IQ) in 72 patients selected because of a history of severe hypoglycemia or hypoglycemia unawareness (36). This therapy offers the advantage of avoiding the invasive procedure associated with IT (which now typically involves only minor complications) and the use of immunosuppressants (with data from our study suggesting no increased oncogenic risk, though infection risks and other adverse effects have not been studied). Additionally, the cost is likely lower, as the long-term costs of IT are still under investigation (37). AID therapy could, therefore, serve as a bridge (for patients who accept it) before considering ITA (38). It is important to note that the decision should be made jointly by the patient and physician, weighing the benefits and risks of both therapeutic approaches. Currently, AID data in patients living with T1D and kidney transplant are not available, with IT remaining the most validated option for these patients as they are already receiving immunosuppressive maintenance due to their kidney transplant.

Limitations

Several limitations in our study should be noted. First, a randomized trial with such a long follow-up was hardly feasible, which is the reason why we opted for an external control design. However, the latter does not guarantee between-group comparability. We have built the control group using a national health care database covering almost the entire French population, which is a strength of this study, but some key variables are missing, including metabolic data, laboratory results (e.g., HbA_{1c}, GFR), and sociodemographic data (e.g., BMI, tobacco consumption, exercise). Moreover, although a better cancer classification would have been invaluable information, notably for skin cancers, there is no specific cancer identification algorithm validated in the SNDS to date. Therefore, we decided to reproduce what was already done and studied in the literature (i.e., breast, colorectal, pulmonary, and prostate cancers) and classified other cancers as "other." As we could not better classify cancer type in the control group, we applied the same classification in the experimental group to avoid a possible misclassification. We partially addressed this limitation with the use of proxies to approximate these missing variables (e.g., two hospitalizations for diabetes complications in the year prior to inclusion as a proxy of unstable diabetes). With the emergence of several T1D cohorts, access to metabolic data could provide a new, comprehensive understanding of patient outcomes.

Second, dates of inclusion and follow-up times were not identical between the two groups as the SNDS starting point was 2006 and the first patient included in the intervention group was in 1999. As best we could, we restricted our control group to have contemporary patients with a sufficient history of diabetes (5 years) and at least 10 years of follow-up (i.e., inclusion between 2011 and 2012). However, with the median duration of diabetes in the intervention group was 31.6 (ITA) and 32.6 (IAK) years, we can assume that the intervention group patients were probably in a more advanced diabetes stage than the control patients, which might underestimate the observed IT effect. Similarly, for the IAK analysis, the matching was not optimal (as shown by large SMDs) and led to imbalance of prognostic factors

between groups, which seemed in favor of the control group and, thus, potentially underestimated the observed benefit of IT.

Third, the study cohorts were small, with <100 patients in experimental groups. Thus, the number of observed events were low, and we cannot exclude a lack of power to detect an excess risk of cancer. Moreover, even with a low statistical power, we were able to identify a significantly lower risk of the primary composite outcome, which strengthens the hypothesis of a genuinely favorable benefit of IT on the risk of diabetes complications or mortality. In the present situation, use of a synthetic control group permitted us to compare the patients who received an IT during clinical trials with patients with T1D with ongoing insulin therapy, the main strength of which is the possibility of matching patients on several risk factors to include and compare them as close as possible on known and measurable risk factors (39). Nevertheless, like every observational study, use of an external control group is subject to biases and unmeasurable residual confounding on every factor, a limit largely discussed before (39).

Fourth, we did not match patients on their cancer history due to a lack of available data; thus, we recommend cautious interpretation of the secondary outcome results. Moreover, in the experimental group, patients with a history of neoplasia in the previous 5 years could not be included, whereas we did not have this exclusion criterion in the control group, possibly selecting patients at higher risk of relapse in the control group. The absence of an excess risk of cancer, although statistically significant, needs to be assessed more thoroughly in a study that considers matching on this criterion. Another common complication of immunosuppressive treatments is the risk of infection. We could not study this due to the lack of a validated algorithm to obtain comprehensive data in the SNDS. Moreover, the absence of accurate data on the day-to-day immunosuppressive regimen in the SNDS made it difficult to draw any conclusions at this stage. Therefore, this study does not provide insight into this type of complication and would necessitate further investigation.

Finally, all patients in the experimental group (IT) were transplanted as part of clinical trials, with strict inclusion/exclusion criteria (i.e., neoplasia history, basal GFR, HLA hyperimmunization) and close monitoring. Now that this therapy is part of standard care, it would be valuable to investigate whether real-world data from newly transplanted patients confirm these findings.

Conclusion

In conclusion, this externally controlled study suggests a long-term benefit of ITA and IAK on a composite outcome of death, cardiovascular complications, or dialysis, with no significant increase in the risk of cancer despite the use of immunosuppressive drugs. Despite the inherent challenges and limitations, the insights gleaned from this study contribute to the growing body of evidence supporting the positive impact of IT on long-term patient outcomes. Moving forward, continued research efforts are warranted to further elucidate the mechanisms underlying the observed outcomes and to optimize the therapeutic approach for patients with T1D and unstable glucose control.

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