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Austrian Institute for
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GmbH

Islet cell transplantation for chronic pancreatitis, type 1 diabetes, with and without kidney transplantation

Systematic Review

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Vienna, March 2025

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List of abbreviations

AE ..... adverse event
BMI ..... body mass index
CP ..... chronic pancreatitis
CT ..... computed tomography
DKD ..... diabetic kidney disease
eGFR ..... estimated glomerular filtration rate
EORTC ..... European Organisation for Research and Treatment of Cancer
EUS ..... endoscopic ultrasound
GFR ..... glomerular filtration rate
GRADE ..... Grading of Recommendations, Assessment, Development, and Evaluations
HbA1c ..... haemoglobin A1c
Hg ..... haemoglobin
HLA ..... human leukocyte antigen
HRQoL ..... health-related quality of life
HTA ..... Health Technology Assessment
ICT ..... islet cell transplant
MRI ..... magnetic resonance imaging
NICE ..... National Institute for Health and Care Excellence
NRSI ..... non-randomised study of intervention
NS ..... not significant
OGTT ..... oral glucose tolerance test
RCT ..... randomised controlled trial
RoB2 ..... Risk of Bias 2
ROBINS-I ..... Risk Of Bias In Non-randomised Studies of Interventions
SAE ..... serious adverse event
SF-12 ..... 12-item short-form survey
SF-36 ..... 36-item short-form survey
T1D ..... type 1 diabetes
UK ..... United Kingdom
US ..... United States
VAS ..... Visual analogue scale
YLD ..... years lived with disability

Executive Summary

Introduction

Health Problem

Chronic pancreatitis (CP) and type 1 diabetes (T1D) are diseases affecting the pancreas. CP is associated with extensive inflammation and scar tissue formation, and T1D is associated with autoimmune destruction of the insulin-producing β-cells. Globally, the point prevalence of CP and T1D is 74.77 and 248.58 per 100,000 population, respectively. Both conditions have significant impacts on patients. CP can be associated with intractable pain and reduced quality of life. A lack of effective disease management in T1D can result in severe hypoglycaemia, diabetic ketoacidosis leading to disability or death without treatment and disease management in patients with T1D.

indications: chronic pancreatitis (CP) & type 1 diabetes (T1D)

destroy insulin-producing ß-cells

Description of Technology

Islet cell transplantation (ICT) involves the isolation of islet cells from a patient's own pancreas (autologous transplant, commonly the source for CP patients) or from a donor pancreas (allogenic transplant, for T1D patients). The isolated islet cells are infused into the hepatic portal vein, where they continue to produce insulin for ongoing glycaemic control. This is typically performed with a pancreatectomy in CP patients to replace functional pancreas tissue removed during surgery. For T1D, ICT aims to replace the use of exogenous insulin and can be provided with or without a kidney transplant in patients with diabetic nephropathy. This therapy is an alternative to the more invasive option of pancreas tissue transplantation. Multiple infusions may be needed.

islet cell transplantation (ICT):

autologous for CP

allogenic for T1D

Method

A systematic search was conducted to evaluate the effectiveness and safety of islet cell transplantation compared with medical management or pancreas transplant. Multiple databases were searched from inception to 14 December 2024, in addition to a hand search of two health technology assessment (HTA) reports. The search was limited to prospective articles published in English or German, to randomised controlled trials (RCTs), non-randomised studies of interventions (NRSI) and case series conducted in humans. Two authors independently conducted study selection, data extraction and quality appraisal. The quality of the included studies was assessed using the RoB2 (Cochrane Risk of Bias 2) tool and the ROBINS-I (Risk of Bias In Non-randomised Studies Of Interventions) tool, and the certainty of the evidence was rated according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

systematic literature search

Results

Available evidence

CP: 3 case series

For CP, three case series were included.

T1D: 2 populations

The T1D group was separated into two populations: studies that included patients with a kidney transplant and those without.

T1D with kidney transplant (Tx): 1 RCT, 2 NRSI, 3 case series

For the population of kidney transplantation with ICT, one RCT comparing ICT with insulin therapy, one NRSI comparing the same populations, and one additional NRSI comparing ICT with kidney transplant to ICT alone were identified, in addition to three case series for ICT.

T1D without kidneyTx: 1 NRSI, 2 case series

For T1D patients without a kidney transplant, one NRSI comparing ICT with pancreas transplant and two case series were included.

Clinical effectiveness

Chronic pancreatitis

CP: evidence limited

The evidence-base for CP was limited to three single-arm case series. Overall, the strength of the evidence for the safety and effectiveness of ICT for CP is very low.

stable blood sugar levels over several years

Across three prospective single-arm studies, glycaemic control (haemoglobin A1C [HBA1c], C-peptide and fasting blood glucose) in ICT patients who underwent total pancreatectomy was stable compared to baseline measures up to three years post-transplant. Insulin independence ranged from 19-78% at short-term timepoints, with 17.6% of participants remaining insulin independent in one study at ten years.

reduction in pain

There were significant reductions in reported pain following ICT and pancreatectomy were reported at up to three years follow-up, as well as reductions in analgesia and morphine equivalent dose. The case series reported improvements health-related quality of life (HRQoL) measures at two years in the domains of global and functional health ($p<0.01$). There were also improvements in all domains of the pancreas-specific quality of life assessments ($p<0.01$).

better quality of life

Type 1 diabetes with kidney transplant

T1D with kidneyTx: evidence very low

One RCT, 2 NRSIs and three single-arm case series were available for the population of T1D patients with severe hypoglycaemia and kidney transplant. Overall, the strength of evidence for ICT in patients with T1D and kidney transplant compared with insulin therapy or compared to ICT without kidney transplant is very low.

RCT: ICT + kidneyTx vs. insulin therapy

Evidence from one RCT showed significantly reduced HbA1c ($p<0.0001$) and a significantly larger proportion of patients recording an HbA1c level of >7% ($p<0.0001$), revealing more optimal glycaemic control in ICT patients compared to those undergoing conventional insulin therapy at six months. There were no significant reductions in fasting blood glucose between the two patient groups; however, a significant reduction in hypoglycaemia events was recorded for ICT patients. Over 50% of patients in the ICT population achieved insulin independence and approximately 93% of patients had a functioning islet graft at twelve months post-transplant. Kidney function (higher estimated glomerular filtration rate [eGFR]) was also significantly improved in ICT patients compared to insulin therapy patients at twelve months.

>50 % of ICT-group achieved insulin independence after 1 year

Measurements of HbA1c ($p<0.0001$), C-peptide (p value not provided), hypoglycaemia (no changes between groups) and insulin independence ($p=$not significant [NS] between groups) indicate similar or improved glycaemic control within patients who receive a kidney transplant in addition to ICT, compared to patients who receive ICT alone. Insulin independence and islet graft function was similar at eight years follow-up, and kidney function was slightly improved in patients who received a kidney transplant.

NRSI: ICT + kidneyTX vs. ICT alone; similar insulin independence between groups

In an NRSI comparing outcomes of ICT with insulin therapy in patients with T1D, there were significant decreases in overall HbA1c ($p<0.01$), number of hypoglycaemic events ($p<0.05$), and reduced requirement of exogenous insulin ($p<0.0001$) for up to three years. There was similar fasting blood glucose in both groups ($p<0.05$ at up to three years).

NRSI: ICT + kidneyTx vs. insulin therapy

ICT: significant less exogenous insulin

Three single-arm studies showed statistically significant reductions in HbA1c and insulin requirements for up to ten years post-transplant ($p<0.01$). For quality of life, there were improvements in SF-36 general health perceptions ($p<0.008$) and health transition ($p<0.001$) compared with insulin therapy alone, and improvements from baseline for diabetes distress scores ($p\leq0.019$), the Hypoglycaemia Fear Score ($p\leq0.002$) and the EuroQOL overall health state ($p<0.001$ at one year).

3 case series: HBA1c & insulin requirements reduction

Type 1 diabetes without kidney transplant

One NRSI (comparing ICT to pancreas transplant) and two case series were identified for T1D patients (with no kidney transplant). Overall, the strength of evidence for ICT in patients with T1D (without kidney transplant) compared with pancreas transplant or insulin therapy is very low. It is noted that patient selection differed in the NRSI for ICT and pancreas transplant patients, and expert opinion has noted that the populations considered for ICT or pancreas transplant is different and that there are inherent differences in the invasiveness of the procedures. The results of this study should be considered with this in mind.

T1D without kidneyTx:

evidence very low

1 NRSI: ICT vs. pancreasTx,

2 case series

Glycaemic control was poorly reported in the NRSI, with no HbA1c, fasting blood glucose or hypoglycaemia outcomes provided. At one-month post-transplant, a greater proportion of patients were insulin-independent in the pancreas transplant group compared to the ICT group (76% versus 57%, p value not reported), with the authors suggesting this is as a result of a delay in the ICT to produce insulin.

insulin independence in 1 NRSI: 76 % ICT vs. 57 % pancreasTx

Case series evidence indicated high C-peptide levels (>0.3ng/ml) in 70–94% of patients, and a reduction in hypoglycaemic events ($p<0.01$) at one to two years. Insulin independence varied across two case series, reducing to 5% at three years in one study. Renal function (eGFR and creatinine clearance) reduced from baseline ($p<0.0001$ and $p=0.06$, respectively). In one case series, HbA1c levels were significantly reduced at one year ($p<0.0003$), with 67% of patients maintaining HbA1c levels at <6.5% at two years ($p=0.02$).

insulin independence varied across case series

Safety

T1D with kidney transplant

In the RCT, there were procedure-related complications in 19.1% and adverse events (AEs) in 42.6% of ICT and kidney transplant patients. For insulin-only patients, there was one recorded serious AE (SAE) in the RCT, and ten grade three and one grade four SAEs reported in the NRSI. One NRSI reported SAEs in 56% and 62.5% of patients in the ICT alone and ICT with kidney transplant groups, respectively.

procedure-related complications in 19 % in 1 RCT

T1D with no kidney transplant

No included study described overall complication rates. Reported AEs were procedural- and immunosuppression-related. In the NRSI, there were more procedure-related AEs in the pancreas transplant group compared with the ICT group (p value not reported). Pancreas transplant patients reported more cytomegalovirus reactivation ($p<0.0001$), but there were no differences in other AEs (e.g. infection, kidney function).

procedural- and immunosuppression related AEs

Upcoming evidence

In patients with CP, one RCT and one randomised pilot trial of patients are underway for ICT and ICT plus concomitant transplantation of mesenchymal stem cells and omental pouch islet cells, respectively. These studies are being conducted in the United States (US).

CP: 2 ongoing trials

For T1D, a randomised, prospective multicentre study is underway investigating ICT compared to insulin therapy for patients with brittle T1D. Separately, a single-centre trial is underway investigating ICT via the hepatic portal vein, comparing it to ICT into the omentum. These trials are ongoing in France and Italy.

T1D: 2 ongoing trials

Discussion

There is a lack of prospective RCTs comparing ICT with alternative therapies, across all populations.

lack of prospective evidence

There were few comparative studies and outcomes were inconsistently reported across studies and populations, limiting the conclusions able to be drawn. Evidence for the population of patients with CP and total pancreatectomy was limited to single-arm studies.

inconsistently reported outcomes across studies

For this review, evidence was restricted to prospective studies that were structured to limit problems associated with prospective research, such as a lack of consistency in patient selection and outcomes reporting. Unfortunately, the included studies remained limited in the overall quality assessment conducted via GRADE. However, it is unlikely that retrospective studies would materially change the overall evidence base.

evidence restricted to prospective studies

Further long-term RCT evidence of patient-relevant outcomes across all relevant populations will add to the existing evidence base.

long-term RCT evidence needed

Conclusion

In patients with CP after total pancreatectomy, the available evidence from three case series was of very low certainty. Although ICT may improve pain, stabilise glycaemia and improve HRQoL over follow-up periods up to ten years, most patients continue to require insulin therapy. Comparative benefits of ICT relative to other interventions remain uncertain.

CP: no available comparative benefits to standard therapy with very low certainty of evidence

For patients with T1D who have received a kidney transplant, ICT demonstrated some improvement in glycaemic control when compared with insulin therapy, but graft survival declined over seven to eight years. The quality-of-life measures improved in these patients. However, procedural complications and AEs were also observed. The overall certainty of evidence was also very low. However, evidence from a single RCT with small patient numbers showed significant improvements in glycaemic scores (HBA1c and severe hypoglycaemia).

T1D with kidneyTx: indicated significant benefit with very low certainty of evidence

For T1D without kidney transplant, the certainty of the evidence from one non-randomised study and two case series was also very low. While some measures of glycaemic control improved, reported outcomes for insulin independence and graft survival varied. At one month, ICT resulted in inferior insulin independence compared with pancreas transplant but fewer AEs; quality of life data was not reported.

T1D without kidneyTx: unclear evidence of benefit with very low certainty of evidence

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Bauchspeicheldrüse (Pankreas) = endokrines und exokrines Organ

zuständig für Bildung von Insulin

wichtig für Blutzuckerkontrolle

Die Bauchspeicheldrüse (das Pankreas) ist ein exokrines und endokrines Organ, das sich im hinteren Teil des Rückens und der oberen Bauchwand befindet. Das Pankreas ist eng mit der Milz, der Gallenblase und dem Zwölffingerdarm des Dünndarms verbunden. Die Bauchspeicheldrüse besteht überwiegend aus Azinuszellen (85 % des Pankreasgewebes), die Enzyme wie Trypsin, Lipase und Amylase in den Zwölffingerdarm absondern, die bei der Verdauung von Proteinen, Fetten und Kohlenhydraten helfen. Die Langerhans-Inseln, die 1-2 % der gesamten Pankreasgewebsmasse ausmachen, haben eine endokrine Funktion. Die Betazellen der Langerhans-Inseln sezernieren Insulin, das den Blutzuckerspiegel beeinflusst, indem es die Aufnahme und Speicherung von Glukose in der Leber, im Fettgewebe und in den Muskeln bewirkt. Die Alphazellen der Inseln sezernieren Glukagon, um die Freisetzung von Glukose aus dem Speicher zu veranlassen, während die Delta-, Pankreaspolypeptid- und Epsilon-Zellen der Inseln jeweils Somatostatin, Pankreaspolypeptid und Ghrelin sezernieren. Bei gesunden Patient:innen arbeiten diese Zellen zusammen, um den Blutzuckerspiegel zu kontrollieren.

chronische Pankreatitis (CP) und Typ-1-Diabetes (T1D):

erhebliche gesundheitliche Beeinträchtigung

Die chronische Pankreatitis (CP) und der Typ-1-Diabetes (T1D) sind Erkrankungen, die mit erheblichen gesundheitlichen Beeinträchtigungen einhergehen. In Österreich liegt die Prävalenz für CP bei 192,55 und für T1D bei 615,04 pro 100.000 Einwohner:in. Bei CP kommt es in Folge von ausgedehnten Entzündungen und Narbenbildung im Pankreas zu hartnäckigen Schmerzen und einer verminderten Lebensqualität (LQ) aufgrund anhaltender Komplikationen. T1D ist durch eine autoimmune Zerstörung der insulinproduzierenden Betazellen gekennzeichnet. T1D-Patient:innen sind ohne angemessene Behandlung und Krankheitsmanagement dem Risiko schwerwiegender Hypoglykämien und diabetischer Ketoazidosen ausgesetzt, die zu schweren Behinderungen oder sogar zum Tod führen können.

viele Risikofaktoren für CP und T1D

Zu den Risikofaktoren für CP gehören familiäre Vorbelastung, übermäßiger Alkoholkonsum, Rauchen, Hyperkalzämie, Diabetes und die Einnahme bestimmter Medikamente, wobei viele Fälle keine definierte Ursache haben. Die Entwicklung von T1D wird mit genetischen Veränderungen im HLA-Gen, bestimmten Infektionen, einer gestörten Darmflora und Umweltfaktoren in Verbindung gebracht.

Beschreibung der Technologie

IZT umfasst Ersatz funktionaler β-Zellen, die durch Krankheit, chirurgische Entfernung oder Autoimmunzerstörung verloren gegangen sind

Die Inselzelltransplantation (IZT) umfasst die Isolierung von Inselzellen aus der Bauchspeicheldrüse der Patient:innen selbst (autogene Transplantation, häufig bei CP-Patient:innen) oder aus einer Spenderbauchspeicheldrüse (allogene Transplantation, für T1D-Patienten:innen). Nach der Isolierung und Aufbereitung werden diese Zellen in die Pfortader injiziert, wo sie im Laufe der Zeit beginnen Insulin zu produzieren. Bei CP-Patient:innen wird dies typischerweise in Verbindung mit einer Pankreatektomie durchgeführt, um funktionelles Pankreasgewebe zu ersetzen, das während der Operation entfernt wurde. Bei T1D zielt die IZT darauf ab, den Einsatz von exogenem Insulin zu ersetzen bzw. reduzieren und kann auch bei Patient:innen mit diabetischer Nephropathie mit oder ohne Nierentransplantation durchgeführt werden.

Methoden

Sicherheit und Wirksamkeit von IZT

Dieser Bericht bewertet die Sicherheit und Wirksamkeit der IZT bei Patient:innen mit vollständiger Pankreatektomie (Population 1), Patient:innen mit TD1, Hypoglykämie und Nierentransplantation (Population 2), sowie bei Patient:innen mit TD1 und Hypoglykämie (ohne Nierentransplantation, Population 3).

systematische Literatursuche

Es wurde zunächst eine systematische Literatursuche in den Datenbanken Medline, Embase, der Cochrane Library und beim International Network of Agencies for Health Technology Assessment (INAHTA) durchgeführt. Zusätzlich erfolgte eine Handsuche in zwei HTA-Berichten. Die Suche beschränkte sich auf prospektive Studien in englischer oder deutscher Sprache, randomisierte kontrollierte Studien (RCTs), nicht-randomisierte Interventionsstudien (NRSI) und Fallserien.

Bewertung der Qualität der Studien

Die Studienauswahl, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden von zwei Autorinnen unabhängig voneinander durchgeführt. Die Bewertung der Vertrauenswürdigkeit der eingeschlossenen RCTs erfolgte mit dem Cochrane Risk of Bias Tool v.2 (RoB2), die Bewertung der nicht randomisierten Studien mit dem Risk Of Bias In Non-randomised Studies of Interventions-Tool (ROBINS-I). Für einarmige Studien wurde kein Bias-Risiko (RoB) bewertet, da diese laut Health Technology Assessment Coordination Group für Wirksamkeitsbewertungen kaum relevant sind. Die Vertrauenswürdigkeit der Evidenz wurde nach dem GRADE-Bewertungsschema (Grading of Recommendations, Assessment, Development and Evaluations) eingestuft.

Klinische Wirksamkeit

entscheidungsrelevante Wirksamkeitsendpunkte

Zur Bewertung der klinischen Wirksamkeit wurden folgende Endpunkte als *entscheidungsrelevant* definiert:

- Kontrolle des Blutzuckerspiegels (alle Populationen, z. B. HBA1c, C-Peptid)
- gesundheitsbezogene Lebensqualität (alle Populationen),
- Überleben der Inselzell-Transplantate (alle Populationen),
- post-operativer Medikamentenkonsum (Population 1),
- post-operativen Schmerzen (Population 1)
- Funktion des Nirentransplantats (Population 2).

Sicherheit

entscheidungsrelevante Sicherheitsendpunkte

Zur Bewertung der Sicherheit wurden folgende Endpunkte für alle Populationen als *enscheidungsrelevant* definiert:

- unerwünschte Ereignisse (AE)
- Mortalität.

Ergebnisse

Chronische Pankreatitis

Verfügbare Evidenz

CP:

3 Fallserien

60-166 Pat.

24-125 Monate Nachbeobachtung (FU)

Für CP (Population 1) wurden drei Fallserien in die Analyse einbezogen. Bei der Literaturrecherche wurden keine relevanten Studien für Patient:innen unter 18 Jahren gefunden, weshalb die vorliegende Arbeit nur Erwachsene einschließt. Die einarmigen Studien wurden in medizinischen Zentren durchgeführt und schlossen zwischen 60 und 166 Patient:innen ein. Die Nachbeobachtungszeit betrug 24-125 Monate. Die Inselzellen waren autogener Herkunft und die Transplantation wurde zusätzlich zu einer totalen Pankreatektomie durchgeführt. Das Durchschnitts- und Medianalter der Studienteilnehmer:innen war zwischen 41,1 und 44,0 Jahren, wobei der Anteil der Frauen in den Studien zwischen 62 und 65 % lag. Der mittlere und mediane BMI der Patient:innen in den einzelnen Studien lag zwischen 22,7-26,6 kg/m^2.

Vertrauenswürdigkeit der Evidenz

3 Fallserien: hohes RoB

Die eingeschlossenen Fallserien wurden alle mit einem hohen RoB eigestuft. Die Vertrauenswürdigkeit für CP ist daher insgesamt als sehr gering einzustufen.

Klinische Wirksamkeit & Sicherheit

starke Unterschiede in Insulinunabhängigkeit zwischen Studien

Bei Patient:innen mit CP blieben die wichtigsten Parameter zur glykämischen Kontrolle – HbA1c, C-Peptid und Nüchternblutzucker – nach IZT und Pankreatektomie weitgehend konstant. Die Insulinunabhängigkeit variierte erheblich zwischen den Studien: 19 % bis 78 % der Patient:innen benötigten in den ersten Jahren nach der Transplantation kein bzw. nur sehr wenig exogenes Insulin. Eine Studie zeigte, dass 17,6 % der Patient:innen auch nach zehn Jahren noch insulinunabhängig waren. Der Großteil der Patient:innen war allerdings in unterschiedlichem Ausmaß auf eine Insulintherapie angewiesen.

Verbesserungen beim Schmerzempfinden

Beim Schmerzempfinden der Patient:innen zeigten die Studien statistisch signifikante Verbesserungen. Im Vergleich zum Ausgangswert vor der Operation verbesserten sich die Schmerzwerte im SF-36-Fragebogen in einer Fallserie von 25,2±19,3 vor IZT auf 57,4±25,7 nach einem Jahr. In einer weiteren Fallserie verminderten sich die Schmerzen der visuellen Analogskala (VAS) deutlich nach einem Jahr (n=79: 2,2), zwei Jahren (n=40: 2,1) und drei Jahren (n=27: 1,9) im Vergleich zu vor IZT (n=116: 5,7). Nach dem Eingriff benötigten 71 % der Patient:innen einer Studie keine Schmerzmittel mehr und in einer anderen Studie wurde die Morphin-Äquivalenzdosis von 118 mg/Tag auf 35 mg/Tag signifikant reduziert.

klinisch verbesserte LQ

Auch die Lebensqualität der Patient:innen verbesserte sich nach IZT und Pankreatektomie . Eine Fallserie, die den EORTC QLQ-30 Fragebogen verwendete, dokumentierte klinisch signifikante Verbesserungen auch noch 3 Jahre (n=13) nach Transplantation in allen funktionellen Bereichen (Zunahme von ≥10 Punkte im Vergleich zum Ausgangswert; n=116) wie globale Gesundheit (34,84 vs. 61,54), körperliche (62,82 vs. 82,05), emotionale (42,17 vs. 71,79) und soziale (30,32 vs. 52,69) Funktionsfähigkeit, sowie auch in symptombezogenen Bereichen (Reduktion von ≥20 Punkte) wie Müdigkeit (72.41 vs. 41.03), Übelkeit (57.90 vs. 24.36), Schmerzen (72.41 vs. 45.16) und Appetitlosigkeit (66.95 vs. 25.64). Der pankreasspezifische EORTC QLQ-PAN26 zeigte klinisch signifikante Verbesserungen (Reduktion von ≥20 Punkte) in fast allen Bereichen, einschließlich Pankreasschmerz, Verdauungssymptomen und Zukunftssorgen.

Sicherheit

Keine der Studien berichtete von Komplikationen oder unerwünschten Ereignissen.

keine unerwünschten Ereignisse (AE)

TD1 mit Nierentransplantation

Verfügbare Evidenz

Für T1D-Patient:innen mit schwerer Hypoglykämie und Nierentransplantation (Population 2) wurden eine RCT, zwei nicht-randomisierte Interventionsstudien (NRSI) und drei einarmige Fallserien einbezogen. In der RCT wurde die IZT mit Nierentransplantation mit einer Insulintherapie verglichen, ebenso in einer NRSI. Eine weitere NRSI verglich die IZT und gleichzeitige Nierentransplantation mit einer IZT ohne Nierentransplantation. Die Studien schlossen zwischen 23 und 72 Patient:innen ein. Die Dauer der Nachbeobachtung lag im Median zwischen sechs und 120 Monaten. Alle IZTs waren allogen und beinhalteten die Entnahme von Inselzellen von verstorbenen Spender:innen.

TD1 mit Nierentransplantation:

1 RCT, 2 NRSI, 3 Fallserien

23-72 Pat.

6 -120 Monate FU

Vertrauenswürdigkeit der Evidenz

Die eingeschlossene RCT wurde mit einem hohem RoB bewertet. Das Verzerrungsrisiko wurde je nach Endpunkt als niedrig bis hoch eingestuft. Bedenken gab es dabei vor allem bei den Aspekten „Abweichungen von den geplanten Interventionen", „Verzerrung durch fehlende Endpunktdaten" und „Auswahl der berichteten Ergebnisse". Die NRSIs wurden mit einem moderaten bzw. hohem RoB bewertet. „Verzerrung aufgrund von Störfaktoren", „Auswahl der berichteten Ergebnisse" und „Verzerrung durch fehlende Endpunktdaten" führten zu den vorliegenden Risikobewertungen. Die Beobachtungsstudien wurden mit einem hohen RoB bewertet. Insgesamt ist die Vertrauenswürdigkeit der Evidenz nach GRADE mit sehr niedrig einzustufen.

1 RCT:
hohes RoB

2 NRSI:
moderates – erhebliches RoB

3 Fallserien:
hohes RoB

Klinische Wirksamkeit

Eine RCT zeigte, dass Patient:innen sechs Monate nach IZT im Vergleich zur konventionellen Insulintherapie eine deutlich bessere glykämische Kontrolle aufwiesen, mit signifikant niedrigeren HbA1c-Werten [5,6 % (38 mmol/mol) für IZT vs 8.2 % (66 mmol/mol) für Insulintherapie, p<0·0001]. 92 % der IZT-Patient:innen und 36 % der Patient:innen mit konventioneller Therapie erlebten bis zu einem Jahr nach der Transplantation keine schweren Hypoglykämien. Eine Insulinunabhängigkeit wurde von 59 % der IZT-Patient:innen nach einem Jahr erreicht, sank jedoch mit der Zeit wieder. Nach zwölf Monaten wiesen noch 93 % der Studienteilnehmer:innen ein funktionierendes Inseltransplantat vor. Die Nierenfunktion (höhere glomeruläre Filtrationsrate [GFR]) war bei IZT-Patient:innen im Vergleich zu Patient:innen mit Insulintherapie insgesamt erhöht, was sich in einer höheren GFR nach zwölf Monaten zeigte (71.8 ml/min vs. 57 ml/min, kein Vergleich zwischen den Gruppen wurde berichtet).

1 RCT:
IZT vs. Insulintherapie (IT):

Insulinunabhängigkeit:
59 % nach 1 Jahr

Ähnliche Ergebnisse zeigte eine NRSI. Über einen Beobachtungszeitraum von bis zu drei Jahren wiesen Patient:innen nach IZT im Vergleich zu Patient:innen mit konventioneller Insulintherapie signifikant bessere HbA1c-Werte auf: nach einem Jahr (6,1±0,7 vs. 7,9±1,0, p<0,0001), nach zwei Jahren (6,4±1,0 vs. 7,5±0,8, p<0,01) und nach drei Jahren (6,6±1,1 vs. 8,1±1,3, p<0,01). Zudem erlitten die IZT-Patient:innen deutlich weniger Hypoglykämien pro Woche (1. Jahr: 0,3±0,5 vs. 2,6±2,1, p<0,05; 2. Jahr: 0,2±0,5 vs. 2,6±2,1, p<0,001; 3. Jahr: 0,7±1,1 vs. 2,6±2,1, p<0,01) und benötigten signifikant weniger exogenes Insulin (p<0,0001).

IZT vs. IT:
statistisch signifikante Reduktion in HBA1c & Hypoglykämien in 1 NRSI

Bei Patient:innen einer weiteren NRSI, die IZT allein mit IZT und zeitgleicher Nierentransplantation verglich, erreichten die Patient:innen mit zusätzlicher Nierentransplantation öfter optimale HbA1c-Werte unter 7 % (49 % vs. 35 %) und hatten leicht erhöhte C-Peptid-Werte (1.0 ng/mL nach acht Jahren vs. 0.7 ng/mL nach sieben Jahren) sowie weniger hypoglykämische Ereignisse (2 vs. 3). Außerdem wurde beobachtet, dass sich der eGFR bei Patient:innen mit IZT und Nierentransplantation, im Vergleich zu IZT alleine, weniger stark reduzierte (0.7 mL/min/1.73 m^2 vs. 6.9 mL/min/1.73 m^2). Ähnlich viele Patient:innen beider Interventionsgruppen wurden insulinunabhängig (37/48 vs. 16/24). In dieser Studie wurden die Unterschiede zwischen den Gruppen nicht statistisch verglichen, so dass die klinische und statistische Bedeutung dieser Ergebnisse unklar bleibt.

keine Unterschiede bei Blutzuckerkontrolle & Insulinunabhängigkeit bei IZT + Nierentransplantation vs. IZT allein in 1 NRSI

Drei einarmige Fallserien dokumentierten statistisch signifikante Verbesserungen im HBA1c- Wert und Insulinbedarf bis zu zehn Jahre nach IZT. Zudem wurde Verringerung der glykämischen Ereignisse beobachtet.

Verbesserungen bei HBA1c bis 10 J FU in 3 Fallserien

Sicherheit

In der RCT traten bei 19,1 %, der Patient:innen mit IZT und Nierentransplantation, verfahrensbedingte Komplikationen und bei 42,6 % unerwünschte Ereignisse (AE) auf. Schwerwiegende unerwünschte Ereignisse (SAEs) wurden bei 56 % bzw. 62,5 % der Patient:innen mit IZT bzw. IZT und Nierentransplantation in einer NRSI gemeldete. Bei Patient:innen, die nur Insulin erhielten, wurde in der RCT ein SAE und in der NRSI zehn SAE des Grades 3 und ein SAE des Grades 4 gemeldet.

19,1 % verfahrensbedingte Komplikationen und 42,6 % AE in 1 RCT

TD1 ohne Nierentransplantation

Verfügbare Evidenz

Für die Population der T1D-Patient:innen mit schwerer Hypoglykämie ohne Nierentransplantation wurden eine NRSI und zwei Fallserien eingeschlossen. Zwei dieser Studien waren einarmig und wurden in den USA und Kanada durchgeführt, während eine in Italien durchgeführte Studie eine Transplantation von Pankreasgewebe als Vergleichsgruppe vorsah. Die Studien schlossen zwischen 36 und 66 Patient:innen ein. Die Nachbeobachtungszeit reichte von unter zwölf Monaten bis zu einem Median von 41 Monaten. Alle eingeschlossenen Studien untersuchten die allogene IZT.

1 NRSI, 2 Fallserien

36-66 Pat.

12-41 Monate FU

Vertrauenswürdigkeit der Evidenz

Das RoB für die eingeschlossene NRSI wurde mit Hilfe des ROBINS-I-Tools als „kritisch“ bewertet. Bedenken gab es vor allem bei den Aspekten „Verzerrung aufgrund von Störfaktoren“, „Auswahl der Studienteilnehmer:innen“ und „Auswahl der berichteten Ergebnisse“. Die Beobachtungsstudien wurden mit einem hohen RoB bewertet. Insgesamt ist die Vertrauenswürdigkeit der Evidenz nach GRADE mit sehr niedrig einzustufen.

1 NRSI: „kritisches“ RoB
3 Fallserien: hohes RoB

Klinische Wirksamkeit

Über die Kontrolle des Blutzuckerspiegels wurde in der NRSI nur unzureichend berichtet (keine Ergebnisse zu HbA1c, Nüchternblutzucker oder Hypoglykämie). Einen Monat nach der Transplantation waren mehr Patient:innen der Pankreastransplantationsgruppe insulinunabhängig als in der IZT-Gruppe (76 % vs. 57 %).

HBA1c und Hypoglykämien: keine Ergebnisse in 1 NRSI

In einer Fallserie sanken die HbA1c-Werte statistisch signifikant von 7,2 % auf 5,6 % nach einem Jahr, wobei 67 % der Patient:innen nach zwei Jahren HbA1c-Werte unter 6,5 % aufwiesen. Die C-Peptid-Werte lagen bei 70-95 % der Patient:innen über dem Schwellenwert von 0,3 ng/ml. In Bezug auf schwere Hypoglykämien zeigte sich eine deutliche Verbesserung im Vergleich zu vor der Transplantation: Während vor der IZT alle Patient:innen mindestens eine schwere Hypoglykämie im vorherigen Jahr erlebt hatten, waren nach einem Jahr 87,5 % der Patient:innen frei von schweren Hypoglykämien.

frei von schweren Hypoglykämien in 1 Fallserie: 87,5 %

In den Fallserien waren nach einem Jahr 42-52 % der Patient:innen insulinunabhängig, wobei dieser Wert auf 17 % nach zwei Jahren und 5 % nach drei Jahren sank.

Insulinunabhängigkeit reduziert in 2 Fallserien

Die Nierenfunktion wurde nur in den Fallserien erhoben und zeigte einen leichten Rückgang nach der IZT. Die glomeruläre Filtrationsrate (GFR) sank signifikant von 98 ml/min/1,73 m^2 auf 82 ml/min/1,73 m^2 nach zwei Jahren und es wurde eine Abnahme der Kreatinin-Clearance beobachtet. Diese Veränderungen wurden als klinisch signifikant eingestuft.

Nierenfunktion reduziert nach IZT 2 in Fallserien

Zur Lebensqualität wurden in den Studien für diese Patient:innengruppe keine Ergebnisse berichtet.

keine Daten zu LQ

Sicherheit

Hinsichtlich der Sicherheit traten bei der IZT deutlich weniger unerwünschte Ereignisse auf als bei der Pankreastransplantation (13 vs. 41). Insbesondere war die Rate der Cytomegalovirus-Reaktivierung bei ICT signifikant niedriger und es gab weniger verfahrensbedingte Komplikationen wie Bluttransfusionen oder Thrombosen. In den Fallserien wurden verschiedene schwerwiegende unerwünschte Ereignisse berichtet, darunter interventionsbedingte Blutungen und immunsuppressionsbezogene Komplikationen wie Neutropenie und Infektionen.

AE: weniger bei IZT vs. Pankreastransplantation (13 vs. 41) in 1 NRSI

versch. SAEs in Fallserien berichtet

Laufende Studien

Für die Population 1 (Patient:innen mit CP) konnte eine RCT und eine randomisierte Pilotstudie mit 42 bzw. 30 Patient:innen identifiziert werden. Die RCT vergleicht die Ergebnisse der IZT mit und ohne die gleichzeitige Injektion von mesenchymalen Stammzellen. Die randomisierte Pilotstudie vergleicht die Injektion von Inselzellen mit Inselzellen aus dem Mesenterialbeutel oder mit keiner Therapie. Diese Studien werden an Universitäten in den Vereinigten Staaten (USA) durchgeführt.

2 laufende RCTs für CP

Für die Population 2 konnte eine landesweite, französische, randomisierte, prospektive, medizinisch-ökonomische Studie zur Untersuchung der IZT im Vergleich zur Insulintherapie bei 42 Patient:innen identifiziert werden. Weiters wurde eine monozentrische, offene, zweiarmige Phase-II-Studie zur Untersuchung der IZT über die hepatische Pfortader im Vergleich zur IZT in das Omentum mit zwölf Patient:innen identifiziert. Diese Studien sollen in Frankreich und Italien abgeschlossen werden.

2 laufende RCTs für TD1

Diskussion

Evidenz zur IZT

Die Evidenz zur Inselzelltransplantation (IZT) ist bei den eingeschlossenen Patient:innengruppen als sehr niedrig einzustufen. Bei chronischer Pankreatitis (CP) liegt begrenzte Evidenz aus drei prospektiven einarmigen Fallserien vor. Diese zeigen stabile Blutzuckerwerte über mehrere Jahre, Schmerzreduktion und klinisch signifikante Verbesserungen der Lebensqualität. Jedoch fehlen Berichte zu Komplikationen oder unerwünschten Ereignissen. Bei Typ-1-Diabetes mit Nierentransplantation stützt sich die Evidenz auf eine RCT, zwei NRSI und drei einarmige Fallserien. Die RCT und NRSIs zeigen bessere glykämische Kontrolle, Insulinunabhängigkeit und weniger Hypoglykämien. Es wurde eine verbesserte Lebensqualität in mehreren Domänen des SF-36-Fragebogens berichtet, jedoch traten sowohl verfahrensbedingte Komplikationen als auch unerwünschte Ereignisse bei IZT-Patient:innen in der RCT auf. Bei Typ-1-Diabetes ohne Nierentransplantation wurde eine NRSI und zwei Fallserien identifiziert. Kaum Daten liegen zur Blutzuckerkontrolle in der NRSI vor. Die Insulinunabhängigkeitsraten variierten zwischen den Fallserien und Berichte zur Lebensqualität fehlen. Verfahrensbedingte unerwünschte Ereignisse wurden bei Pankreastransplantation öfter als bei IZT beobachtet.

Mangel an vertrauenswürdiger Evidenz

Die begrenzte Anzahl vergleichender Studien und die uneinheitliche Ergebnisberichterstattung schränkt die Aussagekraft der verfügbaren Evidenz erheblich ein. Bei Patient:innen mit chronischer Pankreatitis (CP) fehlen Vergleichsstudien zu alternativen Behandlungen nach Pankreatektomie, und auch bei Typ-1-Diabetes (T1D) mit und ohne Nierentransplantation bestehen Forschungslücken. Insgesamt fehlt es an Evidenz, die auf RCTs basiert, um die patient:innenrelevanten Endpunkte in allen eingeschlossenen Populationen zu bewerten.

systematische Reviews & HTAs

Die bisherigen systematischen Reviews und HTAs zu IZT zeigen eine unterschiedliche Evidenzlage für die verschiedenen Patient:innengruppen. Bei chronischer Pankreatitis wird IZT als Option nach totaler Pankreatektomie in aktuellen Leitlinien empfohlen. Allerdings ist diese Empfehlung beschränkt auf ausgewählte Patient:innen mit therapierefraktären Schmerzen. Die Evidenz basiert überwiegend auf retrospektiven Studien (16 von 21) mit hoher Heterogenität. Bei Typ-1-Diabetes zeigt IZT Verbesserungen in gesundheitlichen Aspekten, wie z. B. Lebensqualität. Auch hier sind die Ergebnisberichte heterogen und konzentrieren sich meist auf glykämische Kontrolle und unerwünschte Ereignisse.

retrospektive Studien unterstützen Ergebnisse prospektiver Untersuchungen

Die vorliegende Übersichtsarbeit konzentrierte sich auf prospektive Studiendesigns. Die retrospektiven Studien, die nicht im Fokus dieser Analyse standen, unterstützen generell die Ergebnisse der prospektiven Studien. So zeigen z. B. retrospektive Langzeitdaten aus Italien und Kanada, dass 32-44 % der T1D-Patient:innen fünf bis sechs Jahre nach IZT noch insulinunabhängig sind. Für CP-Patient:innen zeigen retrospektive Studien eine stabile Blutzuckerkontrolle bis zu zehn bis zwölf Jahre nach IZT. Eine wesentliche Verbesserung der Evidenzlage durch die Einbeziehung retrospektiver Studien ist daher nicht anzunehmen.

Schlussfolgerung

unzureichende Evidenz für Zusatznutzen von IZT bei CP

Für IZT bei Patient:innen mit chronischer Pankreatitis und Pankreatektomie liegt keine Evidenz aus vergleichenden Studien vor. Die Ergebnisse der einarmigen Fallserien weisen darauf hin, dass IZT den Blutzuckerspiegel stabilisieren und die gesundheitsbezogene Lebensqualität für mehrere Jahre verbessern kann. Keine Evidenz liegt zur Sicherheit von ITZ bei CP vor. Die Vertrauenswürdigkeit der Evidenz aus drei Fallserien wurde als sehr niedrig eingestuft.

Evidenz für Zusatznutzen mit sehr geringer Vertrauenswürdigkeit für IZT bei T1D mit Nierentransplantation

Bei Patient:innen mit Typ-1-Diabetes, die eine Nierentransplantation erhalten haben, deutet die Evidenz darauf hin, dass die Inselzelltransplantation im Vergleich zur Insulintherapie die glykämische Kontrolle verbessert sowie Hypoglykämien verringern kann. Das Transplantatüberleben nahm allerdings nach einem Zeitraum von sieben bis acht Jahren ab. Auch verfahrensbedingte Komplikationen und unerwünschte Ereignisse wurden nach IZT beobachtet. Die Vertrauenswürdigkeit der Evidenz war ebenfalls sehr niedrig.

unzureichende Evidenz für Zusatznutzen von IZT bei T1D ohne Nierentransplantation

Bei Typ-1-Diabetes ohne Nierentransplantation war die Vertrauenswürdigkeit der Evidenz aus einer nicht-randomisierten Studie und zwei Fallserien sehr niedrig. Während sich einige Parameter der glykämischen Kontrolle verbesserten, variierten die berichteten Ergebnisse für Insulinunabhängigkeit und Transplantatüberleben. Nach einem Monat führte die Inselzelltransplantation im Vergleich zur Pankreastransplantation zu einer geringeren Insulinunabhängigkeit, aber zu weniger unerwünschten Ereignissen.

Evidenz insgesamt sehr niedrig: Re-Evaluierung ab 2027

Insgesamt lag Evidenz mit sehr geringer Vertrauenswürdigkeit vor, um die Sicherheit und Wirksamkeit der IZT bei CP und Typ-1-Diabetes zu evaluieren. Eine Re-evaluierung wird frühestens 2027 empfohlen.

1 Background

1.1 Overview of the disease, health condition and target population[1]

The target populations for this assessment as per the Classification of Diseases 11th Revision (ICD-11) are paediatric and adult patients with chronic pancreatitis who require a pancreatectomy (ICD11: DC32 Chronic pancreatitis), and adult patients with long-term, severe type 1 diabetes with a kidney transplant (ICD11: 5A10 Type 1 diabetes mellitus, GB61 Chronic kidney disease) or without a concomitant kidney transplant for symptom management (ICD11: 5A10 Type 1 diabetes mellitus).

Indikationen: chronische Pankreatitis (CP), Typ-1-Diabetes (T1D) mit/ohne Nierentransplantation (NierenTx)

The pancreas is an exocrine and endocrine organ located behind the posterior and upper abdominal wall, closely associated with the spleen, gallbladder and the duodenum of the small intestine [13]. The pancreas is predominantly composed of acinar cells (85% of pancreatic tissue) that secrete enzymes such as trypsin, lipase and amylase into the duodenum, which aid in the digestion of proteins, fats and carbohydrates [13]. The islets of Langerhans, comprising 1-2% of the total pancreatic tissue mass serve an endocrine function [13]. The β-cells of the islets of Langerhans secrete insulin, which controls blood sugar levels by inducing the uptake and storage of glucose in the liver, adipose tissue and muscles [14]. The alpha cells of the islets secrete glucagon, to induce the release of glucose from tissue storage, while the delta, pancreatic polypeptide and epsilon cells of the islets secrete somatostatin, pancreatic polypeptide and ghrelin, respectively [13]. In healthy patients, these cells work in unison to achieve glycaemic control.

Bauchspeicheldrüse: endokrines und exokrines Organ

ß-Zellen zuständig für Bildung von Insulin

wichtig für Blutzuckerkontrolle

1.1.1 Chronic pancreatitis and pancreatectomy

Chronic pancreatitis (CP) involves the inflammation of pancreatic tissue with the loss of organ endocrine and exocrine function due to formation of fibrous connective tissue following recurrent inflammatory episodes due to the onset of calcifications, pancreatic duct blockages and the onset of autoimmune conditions or pancreatic tissue trauma [15, 16]. CP typically manifests in patients as abdominal pain, digestive issues and weight loss, typically due to pancreatic exocrine insufficiency due to loss of functional tissue and duct blockages associated with fibrous tissue and calcifications [17]. CP can also induce conditions including type 1 diabetes mellitus (T1D) due to loss of β-cells, metabolic bone disease and pancreatic cancer, which may develop several years after

CP = Entzündung des Pankreasgewebes führt zu Verlust der Pankreasfunktion

starke Schmerzen & verminderte Lebensqualität

[1] This section addresses the following assessment elements:
A0001 – For which health conditions, and for what purposes is the technology used?
A0002 – What is the disease or health condition in the scope of this assessment?
A0003 – What are the known risk factors for the disease or health condition?
A0004 – What is the natural course of the disease or health condition?
A0005 – What is the burden of disease for the patients with the disease or health condition?
A0006 – What are the consequences of the disease or health condition for the society?
A0007 – What is the target population in this assessment?
A0023 – How many people belong to the target population?

disease onset [18]. Typical management of CP involves addressing symptoms and comorbidities. Abdominal pain caused by parenchymal ischemia induced by acinar cell injury or pancreatic duct obstruction results in inflammation and pain [18]. This can be treated with pain medications or antioxidant therapies, often with little benefit to patients, or it can be managed via surgical intervention [18]. Endoscopic interventions to remove duct obstructions or invasive procedures including pancreaticojejunostomy or pancreaticoduodenectomy may be performed in patients who are candidates for invasive interventions [18]. Patients who undergo pancreatic resection may require supplemental insulin if the remaining tissue does not produce enough to maintain normal function [18].

medikamentöse Therapie oder endoskopische Eingriffe, z. B. Pankreatektomie (PankreasTx)

In this report, population one includes adult and paediatric CP patients who have undergone pancreatectomy (ICD11: DC32 Chronic pancreatitis).

Population 1: erwachsene und pädiatrische Pat. mit CP + PankreasTx

Risk factors for the onset of CP include family history and genetic abnormalities, excess alcohol consumption and smoking, diabetes and the use of certain medications, with many cases being idiopathic [17]. Additional risk factors including obesity, autoimmune disease and metabolic causes have also been associated with disease onset [19]. There is no significant difference in the prevalence of CP between males and females [19]. The prevalence of CP is highest between the ages of 60-64 and 45-49 for females and males, respectively [19]. Higher body mass index (BMI), lower levels of activity and poor diet are also associated with increased prevalence of CP [19]. It is suggested that 40-75% of patients with CP require surgical interventions such as pancreatectomy to treat ongoing symptoms and complications associated with the disease [20]. The most common types of pancreatectomy for CP include total pancreatectomy, duodenal-preserving pancreatic head resection, pancreaticoduodenectomy and distal pancreatectomy [21].

Risikofaktoren: u. a. familiäre Prädisposition, Übergewicht, Alkohol

The estimated global point prevalence and incidence for CP is 74.77 and 34.81 per 100,000 population, respectively, while the prevalence and incidence in Austria is estimated at 192.55 and 59.04 per 100,000, respectively, in 2021 according to the Global Burden of Disease (GBD) study [22].

Prävalenz in Österreich (Ö): 192,55 pro 100.000 Einwohner:innen

The estimated global burden of CP is significant. The global estimated number of years lived with disability (YLD) was estimated at 364,447 (186,273 to 612,755) in 2017 [19]. Many CP patients will experience several comorbidities as a result of the condition, including malnourishment due to pancreatic enzyme insufficiency and significant pain requiring analgesia [23]. The overall economic costs of CP remain unclear locally; however, estimates suggest costs exceed £285.3 million annually in the United Kingdom (UK), with each patient suggested to exceed costs of £79,000 per year due to hospital stays, treatment of pain and pancreatic surgery [24]. These figures do not consider the impact of productivity loss and additional costs for ongoing psychosocial and disability costs for patients. Following CP with pancreatectomy, patients have been reported to experience comorbidities including malnutrition and glycaemic events – caused by the lack of functioning pancreatic tissue – and complications and adverse events (AEs) associated with surgery, including thrombotic events, infections and bleeding, resulting in significant ongoing morbidity for patients without appropriate treatment or management [25].

globale Belastung erheblich

Begleiterkrankungen: Mangelernährung und starke Schmerzen

PankreasTx ist mit Komplikationen und Begleiterkrankungen verbunden

1.1.2 Type 1 diabetes

T1D is an autoimmune condition characterised by a complex interaction between innate and adaptive immune systems, where insulin-producing β-cells are targeted and destroyed and chronic inflammation is induced [26]. This severely impacts the ability of the pancreas to produce insulin. Symptoms of T1D include polyuria, polydipsia, weight loss and, in some cases, ketoacidosis; however, these symptoms are sometimes not well defined, particularly in adults with late onset T1D [26]. T1D is diagnosed based on fasting blood glucose concentrations of >7·0 mmol/L or via abnormal oral glucose tolerance testing (OGTT). Due to the heritability of the disease, genetic testing of human leukocyte antigen (HLA) haplotypes may identify a genetic link to the onset of the disease [26]. Environmental risk factors associated with the development of T1D include history of certain infections and dysregulated gut microbiota; nutritional factors may also impact the development of the condition but these are less well defined [27].

T1D: Autoimmunerkrankung, zerstört β-Zellen

Diagnose: Nüchternblutzucker >7,0 mmol/L oder abnormaler oraler Glukosetoleranztest

Typical treatment for T1D involves insulin therapy and consistent blood glucose monitoring [28]. Commonly, insulin pumps are used as an alternative to traditional injections, allowing constant infusion of insulin [28]. Other drugs can be used in addition to insulin for treatment and control of hyper- and hypoglycaemia [28]. Without effective treatment of T1D, comorbidities include diabetic ketoacidosis, microvascular disease and cardiovascular disease [29]. A further complication of T1D is Diabetic Kidney Disease (DKD), which is caused by sustained hyperglycaemia resulting in inefficient shunting of the peri-tubular capillaries, tubule-interstitial hypoxia and tissue death. Further, hypoglycaemia, episodes occurring within patients at an average of twice per week or severely once per year may induce seizures or coma, associated with patient death or disability [30]. Although insulin therapy is an effective treatment for many T1D patients, many experience reduced response to insulin therapy over time [29].

unbehandelt führt T1D zu schwerwiegenden Komplikationen, z. B. diabetische Nierenerkrankung als Folge anhaltender Hyperglykämie

In this report, population two includes adult patients (>18 years) with a confirmed diagnosis of T1D for more than two years with severe hypoglycaemia and chronic renal failure as an indication for kidney transplantation (ICD11: 5A10 Type 1 diabetes mellitus, GB61 Chronic kidney disease). Population three includes adult T1D patients (>18 years) with a confirmed diagnosis of T1D for more than two years with severe hypoglycaemia without chronic renal failure or the need for kidney transplantation (ICD11: 5A10 Type 1 diabetes mellitus).

Population 2: T1D + Hypoglykämie + NierenTx

Population 3: T1D + Hypoglykämie ohne NierenTx

Risk factors associated with the development of T1D include genetic and occasionally lifestyle factors including poor diet and prior infections [27]. Heritability of T1D is often associated with the HLA gene; however, the onset of the disease is associated with a combination of genetic and environmental factors, including infections such as enterovirus and retrovirus infections, which have been associated with higher prevalence of T1D [31]. Nutritional exposure in pregnancy has also been implicated in the development of islet autoimmunity and associated T1D [32, 33]. T1D is most frequently diagnosed in adolescence and is slightly more prevalent in males in the Austrian population [31].

Risikofaktoren: genetische Faktoren, schlechte Ernährung und frühere Infektionen

As of 2021, the global point prevalence and incidence of T1D was 248.58 and 6.73 per 100,000 people, respectively. Within Austria, the prevalence and incidence of T1D is 615.04 and 11.12 per 100,000. Within this population, the prevalence and incidence of chronic kidney disease induced by complications

Prävalenz in Ö: 615,04 pro 100.000 Einwohner:innen

of T1D was estimated at 173.91, and 2.25 per 100,000 people, respectively, in Austria in 2021 respectively [22].

jährliche Kosten für Behandlung in Ö: >3 Milliarden Euro

The annual cost of T1D treatment and management in Austria is anticipated to exceed three billion Euros [34]. The overall cost of T1D treatment is difficult to establish due to the many comorbidities that may develop because of the condition, with each incurring significant costs for treatment and management. The YLD of Austrian T1D patients is 4,205.27 and for patients with T1D-induced chronic kidney disease the YLD is 690.43. Several social, emotional and economic impacts are recognised for T1D patients with severe and ongoing hypoglycaemic episodes [35]. Significant psychological impacts are associated with the distress caused by hypoglycaemic episodes, which can also impact sleep and induce severe and ongoing fear within patients, impacting daily functioning, productivity and quality of life [35].

soziale, emotionale und wirtschaftliche Belastungen

1.2 Current clinical practice[2]

1.2.1 Chronic pancreatitis and pancreatectomy

Leitlinien zur CP-Diagnose, Anamnese und Bildgebung

Recommendations from the United European Gastroenterology guidelines, the British Society of Gastroenterology and the American College of Gastroenterology suggest that upon suspicion that a patient has CP, family and medical history, including symptom onset, alcohol consumption and smoking habits, are assessed in order to commence disease management and treatment and to identify any differential diagnoses [16, 17, 36]. In patients with family history or early onset disease, genetic testing is offered to identify variants [16]. To assist in diagnosis, endoscopic ultrasound (EUS), magnetic resonance imaging (MRI) or computed tomography (CT) may be performed to identify morphological changes, pancreatic calcifications, pseudocysts and pseudoaneurysms indicative of pancreatitis [16, 17, 36]. Pancreatic function tests, including pathological testing of blood and faeces, can be used to further evaluate pancreatic exocrine insufficiency [16]. Nutritional markers are also employed to assess the extent of pancreatic exocrine insufficiency and, in some cases, the efficacy of enzyme replacement therapy where it has been employed in patients who are experiencing nutritional deficits [16, 36].

bei familiärer CP: Gentests

Behandlungsoptionen: Enzymersatz

Treatment options for CP will depend on the symptoms experienced by individual patients. Therapies such as pancreatic enzyme replacement therapy and proton pump inhibitors are employed for malnutrition and malabsorption, in addition to oral supplementation of key vitamins where necessary [16, 36]. In patients with CP-induced diabetes mellitus, patients are treated with lifestyle and dietary interventions; in cases where patients experience severe

[2] This section addresses the following assessment elements:
A0024 – How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025 – How is the disease or health condition currently managed according to published guidelines and in practice?
B0004 – Who administers the technology and the comparators and in what context and level of care are they provided?
B0008 – What kind of special premises are needed to use the technology and the comparator(s)?

hypoglycaemia, insulin therapy and adjuvants are commenced [16, 36]. Some patients may be eligible for endoscopic therapy, where decompression of the pancreatic ducts and drainage of disease complications such as pseudocysts and biliary strictures is utilised to treat pain and exocrine insufficiency [36, 37]. Pain therapies are frequently employed in the treatment of CP due to it often being the first sign of CP onset in patients [16]. Following cessation of smoking and alcohol consumption, pain therapies such as paracetamol, non-steroidal anti-inflammatory medications, tramadol and opioids can be prescribed to treat pain, alongside adjuvant therapies including antidepressants and anxiolytics in certain cases [16, 17, 36]. Nerve blocks, spinal cord simulation and acupuncture can also be employed for pain treatment [16].

endoskopische Gangdekompression

Schmerztherapie mit Analgetika, Nervenblockaden & Akupunktur

Endoscopic therapy and surgical interventions are also employed to treat intractable pain associated with CP [36]. Surgical intervention for the treatment of CP is advised in cases of severe and intractable pain, or in some cases, risk of the onset of pancreatic cancer [16]. Surgical techniques and the degree of pancreatic resection will differ depending on the degree of CP and morphological and pathological features of the pancreas [16]. The aim of pancreatectomy is to remove diseased tissue and/or structures blocking the ducts resulting in pain [36]. Pancreatectomy is indicated in patients who experience intractable pain, those who have small duct disease or an enlarged pancreas head and where previous endoscopic draining procedures have failed [36]. Following surgical intervention, insulin replacement therapy and treatment for pancreatic exocrine insufficiency may need to be commenced depending on the amount and function of remaining pancreatic tissue [16]. Pancreas or islet cell transplantation may also be considered, particularly following pancreatectomy, to replace pancreas function following tissue removal [17].

chirurgische Eingriffe bei starken Schmerzen

Pankreatektomie: Entfernung von erkranktem Gewebe

nach OP: meist Insulin- und Enzymersatz nötig, evtl. Inselzelltransplantation (IZT)

1.2.2 Type 1 diabetes

A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes, and guidance from the National Institute for Health and Care Excellence (NICE), provides recommendations for the diagnosis and treatment of T1D [38, 39]. An established algorithm for the diagnosis of T1D, specifically for white European populations suggests first testing for islet autoantibodies in blood samples, which if positive, suggest patients have T1D [38]. In cases where patients are negative for islet autoantibodies, which can occur in T1D patients, individuals <35 years are tested for monogenic diabetes, and type 2 diabetes symptoms and C-peptide levels are assessed [38]. In individuals aged >35, ongoing symptom monitoring and C-peptide assessment is performed [38]. In both diagnostic groups, if C-peptide levels are <200 pmol/L, T1D may be indicated [38]. Genetic testing may also identify genetic variants that may explain the onset of disease [38].

Diagnose von T1D: Inselautoantikörper im Blut

bei negativem Test: C-Peptid-Messung

C-Peptid <200 pmol/L weist auf T1D hin

Following the diagnosis of T1D, maintaining glucose levels, minimising hypoglycaemia glucose, managing risk factors for comorbidities and minimising the psychosocial burden of disease are of the upmost importance [38, 39]. Typical treatments for T1D include ongoing medical management interventions such as continuous glucose monitoring with electronic devices, exogenous insulin therapy via pump, injection or pens techniques following meals and mimicking normal physiology and education for the management of hyper- and hypoglycaemic attacks if they do occur to prevent serious disability or death [38, 39]. Hypoglycaemic events are a consequence of exogenous insulin use and must be managed appropriately [35]. In cases where hypoglycae-

T1D-Behandlung: Glukosemonitoring, Insulin

Hypo-/Hyperglykämie-Management

bei schwerem T1D: evtl. Transplantation

mic events have induced cognitive changes in patients, education of family, friends and carers to manage such events may also be necessary [35]. Recommendations and education for dietary changes and nutrition therapy, physical activity and comorbidity prevention are also provided for patients [38]. Pancreas and islet transplantation may be considered for patients with severe T1D and hypoglycaemia, with many patients opting for pancreas transplantation also receiving kidney transplantations, especially those with renal disease [38, 39]. However, immunosuppression will be required due to the allogenic nature of the transplant, where pancreas, islet cells and kidney tissue is acquired from donors [38].

1.3 Features of the intervention[3]

1.3.1 Features of the assessed intervention

Inselzelltransplantation (IZT):

Ersatz verlorener β-Zellen

autologe IZT bei chronischer Pankreatitis

allogene IZT bei Typ-1-Diabetes

Islet cell transplantation (ICT) and whole pancreas transplantation and is a technique for disease management for both CP and T1D, and has been used as a treatment option for T1D since the 1980s [40]. Since this time, improvements in islet cell isolation techniques in both human and animal tissue have resulted in improved rates of insulin independence and continued islet cell graft function among patients [41]. Further, clinical trials investigating immunosuppression protocols and isolation methods were refined and identified, leading to improved patient outcomes [41]. The primary role of ICT is to replace the functional β-cells lost due to either a lack of functional pancreatic tissue due to disease or surgical removal in CP, or due to autoimmune destruction of pancreatic tissue and functional β-cells in T1D [42]. ICT can be both autologous or allogenic, with autogenous ICT involving the removal and isolation of islet cells from the patient's own pancreas, which is typical for CP patients, while allogenic ICT involves the isolation of islet cells from donor pancreatic tissue due to the lack of viable tissue from a patient, which is typical for patients with T1D [42].

Gewinnung von Pankreasgewebe: durch Organspende oder chirurgisch entferntes Pankreas

In both cases, ICT involves the procurement of pancreatic tissue either from donor tissue or a patient's pancreas following surgical extraction in CP [43]. The pancreatic tissue is transported to an isolation lab after the tissue is flushed with a preservation solution [43]. The pancreas is dissected, perfused with collagenase solutions to load the pancreatic acinar-islet interface with digestive enzyme, and dissected via mechanical and chemical digestion [43].

[3] This section addresses the following assessment elements:
B0001 – What is the technology and the comparator(s)?
B0002 – What is the claimed benefit of the technology in relation to the comparators?
A0020 – For which indications has the technology received marketing authorisation or CE marking?
B0003 – What is the phase of development and implementation of the technology and the comparator(s)?
B0009 - What supplies are needed to use the technology and the comparator(s)?
B0004 – Who administers the technology and the comparators and in what context and level of care are they provided?
B0008 – What kind of special premises are needed to use the technology and the comparator(s)?
A0021 – What is the reimbursement status of the technology?

Trennung von Inselzellen und exokrinem Gewebe

The solution is cooled, and collagenase binding proteins are added to halt enzymatic digestion [43]. The resulting solution is then purified, separating islets from exocrine tissue, and the remaining cells are cultured for 24-72 hours [43]. Following this, islets are assessed for quality via several parameters including purity, settled tissue volume and sterility [43].

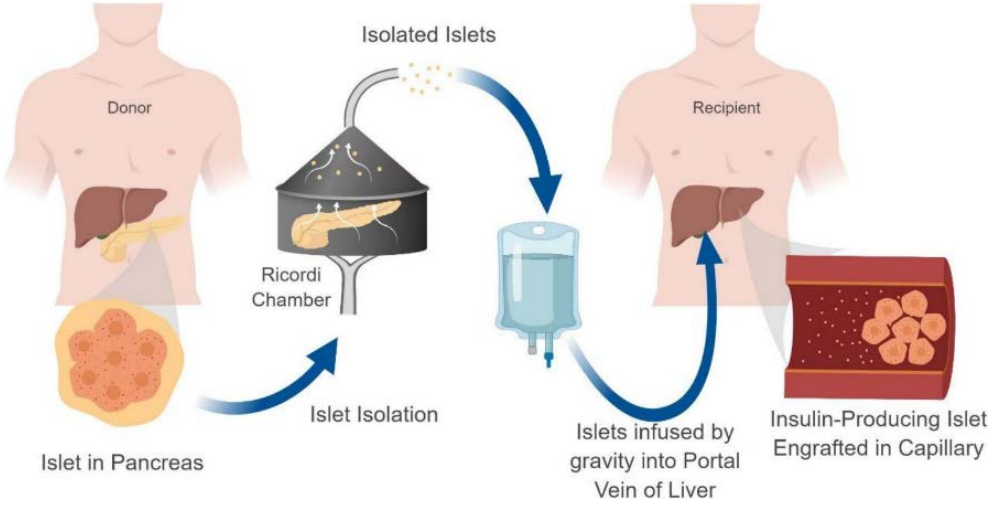


Figure 1-1: Process of islet cell transplantation (Source: Quintana, 2018)

IZT über Pfortader

nach Transplantation: Insulin und unterstützende Medikamente

bei allogener IZT Immunsuppression notwendig

ICT often occurs via the intraportal route, whereby islet cells are transplanted into the hepatic portal vein [43, 44]. This vein can be reached via a percutaneous trans-hepatic access route, which does not typically require extensive surgery or general anaesthesia [43]. Often a concomitant heparin infusion will take place to prevent venous thrombosis during the procedure [43]. In patients receiving allogenic ICT, immunosuppression regimens are required to prevent an autoimmune response against the transplanted islet cells and to achieve insulin independence, where patients do not require exogenous insulin. A variety of immunosuppression regimens have been employed in ICT patients, including drugs such as sirolimus, tacrolimus and daclizumab, with the combination of these drugs being known as the Edmonton protocol [45]. In patients receiving autologous ICT, no immunosuppressive protocol is needed [46]. Patients are provided intravenous insulin and other supportive medicines following transplantation to support implanted islet cells and to promote recovery [46].

IZT und Nierentransplantation:

Immunsuppression bereits vorhanden

ICT can occur within patients with, or simultaneously during kidney transplantation to treat end-stage renal disease typically caused by T1D [47]. For patients with a pre-existing kidney transplant, immunosuppressive protocols are already in place, potentially improving the efficacy of transplanted islet cells [47]. Such procedures are also typically performed concomitantly due to the benefits of glycaemic control induced by ICT preventing the recurrence of diabetic neuropathy within the kidneys [46].

interdisziplinäres Team erforderlich

ICT requires several personnel in the procedural and laboratory aspects. Interventional radiologists, transplant surgeons, anaesthetists and nurses may be required for both the ICT procedure and pancreas removal in certain cases [48]. Several laboratory personnel may also be required for the islet cell isolation protocol.

derzeit nicht im österreichischen Leistungskatalog abgebildet

According to the submission materials, 20 institutions in Austria could carry out ICT within the next twelve months with the expected annual number of procedures being 250 per year. The Austrian hospital benefit catalogue [49] does not include the transplantation of islet cells after pancreatectomy (autologous) or for T1D and/or with/after kidney transplantation (both allogeneic). Therefore, it is not fully reimbursed by the Austrian healthcare system.

1.3.2 Features of the comparators

Therapien bei CP & T1D

Several existing treatment and management options for CP and T1D are available.

CP: symptomabhängige Therapie (Schmerz, Mangelernährung, Diabetes)

Pankreatikoduodenektomie: häufigste OP bei CP

In CP, patients are managed based on presenting symptoms such as pain, malnutrition and pancreatitis-induced diabetes mellitus [16]. In some cases, patients may be prescribed pain therapies or oral enzyme therapies and will be prescribed exogenous insulin in cases where functional pancreatic tissue is minimal [16]. In such cases, treatment will often be prescribed by a primary care provider, gastroenterologist or, in some cases, a pain management specialist [17]. Where medical management is insufficient for treatment of CP patients, open or endoscopic surgical intervention may be considered [16, 17]. Surgeons, endoscopists and gastroenterologists may be involved in performing surgical interventions for CP; surgery can involve both partial or complete pancreas removal [16]. Most frequently, a pancreaticoduodenectomy is performed to remove diseased tissue and resolve pain associated with CP. Following the procedure, patients may require ongoing pancreatic enzyme replacement therapy (PERT) and insulin therapy to replace the activity performed by the pancreatic tissue [16]. Patients with T1D will undergo medical management as previously described, involving ongoing glucose monitoring, insulin therapy and adjuvant therapies as prescribed by an endocrinologist or primary care provider [38].

PankreasTx häufig bei CP und T1D

bei T1D-Pat. mit terminaler Niereninsuffizienz häufig kombinierte Pankreas-Nieren-Transplantation

In some cases, CP and T1D patients are referred for a pancreas transplant, with or without a kidney transplant for diabetic patients with end-stage renal disease due to diabetic neuropathy [50]. Pancreatic transplant in CP is often performed following surgical removal of the diseased pancreas, while for T1D, it is often completed to replace non-functional tissue lost due to autoimmune processes [51]. Pancreas and kidney tissue is transplanted from a donor matched to the patient to prevent organ rejection [52]. Although pancreas transplant techniques can differ, the surgical intervention may involve anastomosis of the donor tissue duodenum to recipient jejunum tissue and anastomosis of surrounding blood vessels for drainage and arterial supply to transplanted tissue [52]. Similarly to ICT, a larger surgical team and several personnel are required for organ procurement, transport and transplantation. Following transplantation of pancreas and kidney tissue, where required, patients will be placed on an immunosuppression regimen to prevent organ rejection and failure [52].

Benefits of islet transplantation over pancreas transplantation

IZT weniger invasiv als PankreasTx; geringeres Risiko für chirurgische Morbidität/Mortalität

There are several cited benefits of ICT over whole pancreas transplantation techniques for both CP and T1D. ICT is typically less invasive than whole organ transplantation and it has been reported to have a lower risk of surgical morbidity and mortality, particularly in T1D patients, where removal of the pancreas is not required, unlike for CP patients who may require abdom-

inal surgery for removal of diseased tissue [51]. Previous studies have identified that insulin independence rates for pancreas transplant patients are comparable over five years, which may suggest similar rates of efficacy between the interventions [46].

patient:innenspezifische Kriterien in Leitlinien

However, several published guidelines have different patient criteria for ICT and pancreas transplant, limiting the direct comparison of these interventions [53, 54].

Table 1-1: Features of intervention and comparators for total pancreatectomy and islet cell transplantation

	Intervention/ technology	Pharmacotherapy comparators	Non-pharmacotherapy comparators
Name	ICT and pancreatectomy	Medical management (e.g. pancreatic enzyme replacement)	Surgical interventions
Proprietary name (manufacturer) of intervention	-	Numerous pharmacological agents available. Specific brand names will not be listed	Drainage procedures, subtotal/ partial pancreatectomy & pancreas transplantation alone

Abbreviations: ICT … islet cell transplantation

Table 1-2: Features of intervention and comparators for type 1 diabetes

	Intervention/ technology	Pharmacotherapy comparators	Non-pharmacotherapy comparators
Name	Allogeneic islet cell transplantation	Insulin replacement therapy (e.g. insulin pump, injection)	Surgical interventions
Proprietary name (manufacturer) of intervention	e.g. Donislecel-jujn, Lantrida™, CellTrans Inc, FDA approved since July 2023	Numerous pharmacological agentsavailable. Specific brand names will not be listed	Pancreas transplantation or pancreas transplantation after/ during kidney transplantation

Abbreviations: FD … Food and Drugs Administration

1.3.3 Patient Selection

unterschiedliche Auswahlkriterien für Patient:innen

Clinical advice has indicated that patient selection differs for pancreas transplant and ICT in patients with T1D. For choice of intervention (use of pancreas transplant or ICT), published guidelines are varied in protocols and detail of patient selection, and differ between pancreas transplant and ICT [53-55]. For example:

- ICT is a treatment of last resort of after the failure of optimal diabetes management, after a failed pancreatic graft, or in selected cases of chronic pancreatitis [56].
- Patient selection should be based on a multidisciplinary team [39, 57, 58].
- Current ICT indications include patients with T1D who are sensitive to exogenous insulin and are suffering from repeated episodes of hypoglycaemia unawareness [58].
- ICT is appropriate for a small group of patients with severe hypoglycaemia, hypoglycaemia unawareness, and brittle diabetes, who have failed to respond to standard treatment and management [59].
- ICT is considered for patients with T1D that are unable to achieve optimal glycaemic control despite optimised conventional therapy [53, 54].

CITR: Leitlinie für IZT + PankreasTx

Members of the Collaborative Islet Transplant Registry (CITR) including the Australian and New Zealand Islet and Transplant Registry and British Transplant Society have published guidelines on ICT and pancreas transplant, including detailed patient selection criteria [53, 54, 60].

wichtige Entscheidungskriterien: Auswirkungen von OP und Immunsuppression

Various issues need to be considered prior to a decision on transplant (pancreas or ICT). Common considerations relevant to the decision to undergo a transplant include the impact of surgery and ongoing impact of long-term immunosuppression. Compared to pancreas transplant, islet transplant can be indicated for some patients [50]. While the surgical risks are less compared to pancreas transplant due to ICT being less invasive, there is still a need for similar levels of immunosuppression [58].

verschiedene Risiken: z. B. Immunsuppression, Thrombosebildung bei Injektion, allogene Immunantwort …

The risk of immunosuppression also needs to be considered. For example, islet cell transplantation is contraindicated in patients with poor renal function due to the detrimental effects of CNI-based (calcineurin inhibitors like cyclosporine and tacrolimus) immunosuppression on kidney function [58]. Intraportal islet cell transfusions are also associated with platelet activation, blood clot formation with portal venous thrombosis, and complement system activation, otherwise known as instant blood-mediated inflammatory reaction. Other issues include allogeneic immune response and autoimmune recurrence [58, 61]. There are also risks of severe adverse events with immunosuppression in pancreas transplant [62]. This is commonly tacrolimus-based regimens and may involve hyperglycaemia and nephrotoxicity [63].

Therapiemöglichkeiten bei Hypoglykämien

In addition to best medical management, pancreas transplant and ICT for patients with T1D, other alternatives for patient management of hypoglycaemic events include insulin pumps, continuous glucose monitors and artificial pancreas (also known as closed-loop insulin delivery systems) [58].

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is islet cell transplantation (ICT) in comparison to medical management or pancreas transplantation in patients with CP or T1D with or without a kidney transplant more effective and safer for glycaemic control, quality of life, reduction in opiate use, immunosuppression complications, AEs and mortality?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

	Population 1	Population 2	Population 3
Population	Adult and paediatric patients with CP who undergo total pancreatectomy[1] (ICD11: DC32 Chronic pancreatitis)	Patients aged >18 years with minimum of 2 years of T1D with severe hypoglycaemia and chronic renal failure[1, 2] (ICD11: 5A10 Type 1 diabetes mellitus, GB61 Chronic kidney disease)	Patients aged >18 years with minimum of 2 years of T1D with severe hypoglycaemia without chronic renal failure[1, 2] (ICD11: 5A10 Type 1 diabetes mellitus)
Intervention	Total pancreatectomy with ICT	ICT with concomitant kidney transplant ICT after kidney transplant	ICT
Control	Medical management (e.g. antioxidant supplementation, pancreatic enzyme replacement, endoscopic decompression/stenting, celiac plexus nerve block, opioid regimens) Drainage procedures (Puestow's, Partington-Rochelle's, Duval's procedures) Subtotal/partial pancreatectomy Pancreas transplantation (alone)	Insulin replacement therapy and adjunct therapies Pancreas transplantation (pancreas-after-kidney transplantation, simultaneous pancreas-kidney transplantation)	Insulin replacement therapy and adjunct therapies Pancreas transplantation (alone)
Outcomes			
Efficacy	Glycaemic control (e.g. HbA1c, C-peptide hypoglycaemia events/unawareness, insulin independence, reduction in insulin dose requirements) HRQoL (SF-36, SF-12, Diabetes Distress Score) Postoperative reduction in opiate use (e.g. morphine equivalents pre-TPIAT and narcotic use post-TPIAT) Postoperative reduction in pain (e.g. visual analogue scale) Islet cell graft survival	Glycaemic control (e.g. HbA1c, C-peptide, hypoglycaemia events/unawareness, insulin independence, reduction in insulin dose requirements) HRQoL (SF-36, SF-12, Diabetes Distress Score) Renal function Islet cell graft survival	Glycaemic control (e.g. HbA1c, C-peptide, hypoglycaemia events/unawareness, insulin independence, reduction in insulin dose requirements) HRQoL(SF-36, SF-12, Diabetes Distress Score) Renal function Islet cell graft survival

Safety	Adverse events (all, serious) Mortality
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials (>20 patients)
Safety	Randomised controlled trials Prospective non-randomised controlled trials (>20 patients) Prospective case-series (>20 patients)

Abbreviations: HbA1c … Haemoglobin A1C; ICD-11 … International Classification of Diseases 11th Revision; ICT … Islet cell transplantation; SF-12 … short-form-12 assessment; SF-36 … short-form 36 assessment.

Comments:

[1] *Australian and New Zealand Islet and Pancreas Transplant Registry. Who needs an islet or a pancreas transplant?*, http://anziptr.org/who-needs-a-pancreas-transplant/ *(n.d.).*

[2] *British Transplantation Society. UK Guidelines on Pancreas and Islet Transplantation. 2019.*

3 Methods

3.1 Research questions

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment. Please refer to Appendix (Table A-18 to Table A-20) for the detailed research questions.

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

Suche nach systematischen Reviews

A preliminary systematic search for systematic reviews (SR) and health technology assessments (HTAs) was conducted in Medline, INAHTA, Embase and the Cochrane Library databases on 12 December 2024 in addition to a hand-search for HTAs to identify the most recent SRs meeting the scope of the present assessment. Consequently, a report from Haute Autorité de Santé (HAS) from 2020, was identified and used as the basis for this report. This SR was used for the purpose of identifying primary studies up to 2020, and an updated search for additional studies was performed on 20 December 2024 [56].

1 HTA-Bericht aus dem Jahr 2020

systematische Suche: Primärstudien, 4 Datenbanken

The systematic literature search was conducted in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- International HTA database (INAHTA)

insgesamt 3.379 Treffer identifiziert

The systematic search was limited to 2020-2024 in English or German. Overall, 3,379 citations were included. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien

To identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) was conducted on 22 January 2025 resulting in 206 potentially relevant hits. The four relevant studies are summarised in the Appendix Table A-17.

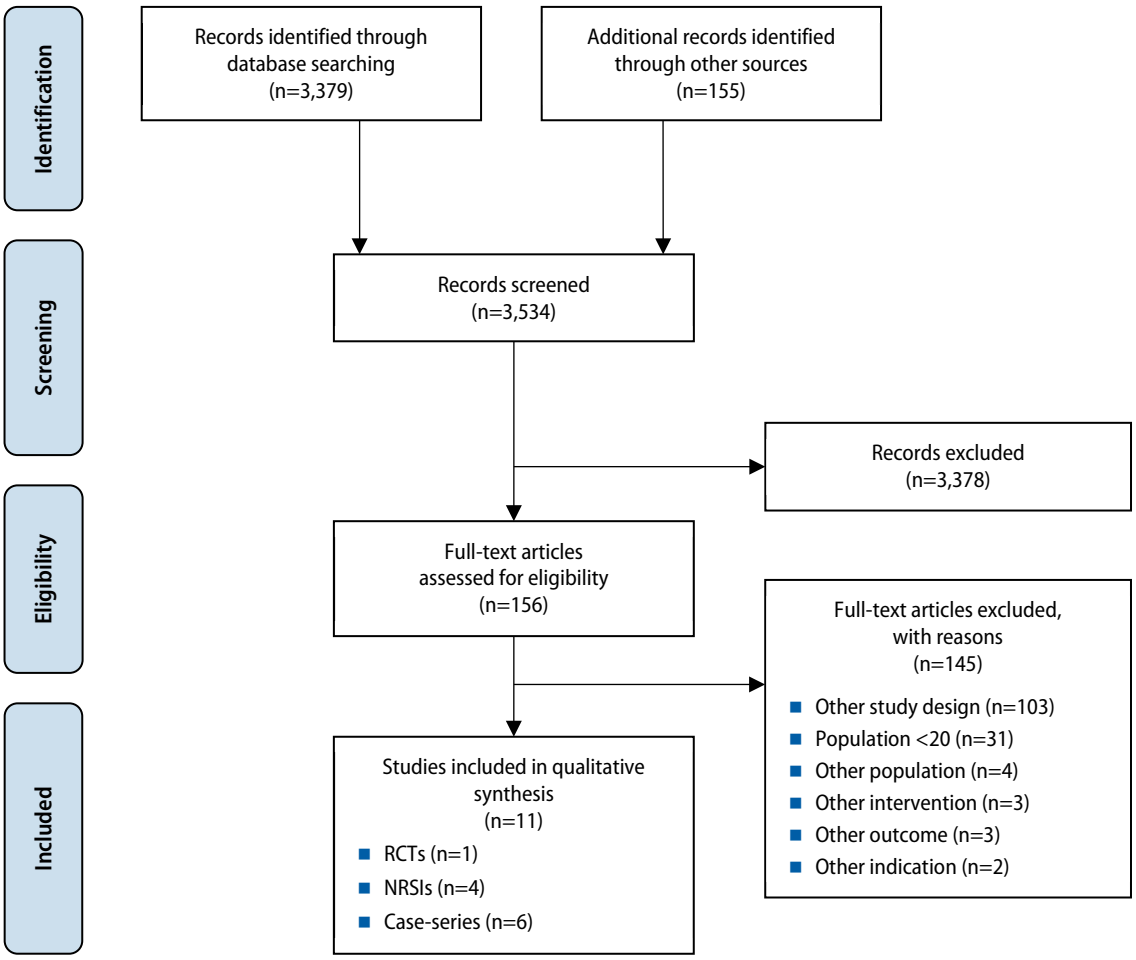
insgesamt 3.534 Publikationen identifiziert

By hand-searching two additional HTA reports, an additional 155 publications were found, resulting in 3,534 hits overall.

3.2.2 Flow chart of study selection

A total of 3,534 studies were identified. Citations were screened by two independent researchers (RH, VH), with an additional researcher screening abstract (GG). The selection process is displayed in Figure 3-1.

Literaturauswahl:
11 Studien eingeschlossen



Abbreviations: NRSI … nonrandomised study of interventions, RCT … randomised controlled trial.

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Risk of Bias: Cochrane RoB 2 und ROBINS-I

The Cochrane Risk of Bias (RoB2) tool for assessment of randomised control trials (RCTs) and the Risk Of Bias In Non-randomised Studies Of Interventions (ROBINS-I) tool for non-randomised study of interventions (NRSIs) were utilised to assess risk of bias (see Table A-8 to Table A-11) [64, 65]. Single-arm studies were not assessed for risk of bias, with study quality assumed to be low due to study design (see Section 5 for details). The certainty of the data was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach [66].

Datenextraktion, RoB, GRADE

One reviewer (RH or VH) extracted relevant data from the included studies into data extraction tables. A second reviewer (RH or VH) cross-checked the data extraction tables for accuracy. Risk of bias assessments were conducted by two reviewers (RH and VH), with differences settled by consensus. One reviewer (KN) analysed the certainty of data using GRADE, and a second reviewer (RH) validated the analysis.

3.2.4 Synthesis

qualitative Synthese der Evidenz

The questions were answered in plain text format with reference to GRADE evidence tables (Table 5-1 to Table 5-4). Results are summarised in Table A-12 to Table A-15.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

The following outcomes were defined as *crucial* to derive a recommendation:

entscheidungsrelevante Wirksamkeitsendpunkte

- **Glycaemic control (all populations):**
  Includes measures such as haemoglobin A1C/glycated haemoglobin (HbA1c), C-peptide, OGTT, fasting blood glucose, hypoglycaemic events, insulin independence, required exogenous insulin amount and ß-score (composite measure of glycaemic control) [67]. Such measures are deemed as a primary measure for ICT efficacy, as ß-cell failure is associated with glycaemic instability [68]. Effective glycaemic control can be achieved through islet cell or pancreatic transplantation or sufficient medical management [68].

  Blutzuckerkontrolle,

- **Health-related quality of life (HRQoL) (all populations):**
  Utilised as a method of assessing the psychosocial outcomes of interventions through several types of assessments including the 12-Item and 36-Item Short Form Health Survey (SF-12/SF-36) and the Diabetes Distress Score (DDS) questionnaire [69]. Such questionnaires assess several domains including health perception, physical functioning, social functioning, life satisfaction and pain [69].

  Lebensqualität (LQ),

- **Islet cell graft survival (all populations):**
  C-peptide, produced as a by-product of insulin, can indicate ongoing graft function and insulin production. Most measures of islet cell graft function asses the proportion of patients achieving a C-peptide reading >0.33 nmol/L, indicating optimal ß-cell activity [70, 71].

  Funktion der Inselzelltransplantate,

- **Postoperative opioid use (population 1):**
  When combined with pancreatectomy, ICT may be used as a method for pain relief in CP patients, reducing the need for pain relief therapies such as opioids [72]. Reduction in use of analgesics can be indicative of pain relief post-pancreatectomy and ICT [72].

  postoperativer Medikamentenkonsum,

- **Postoperative pain (population 1):**
  Pain scores and assessments have been utilised to assess pain resolution following pancreatectomy and ICT in CP patients [73]. Scores using the visual analogue scale (VAS) and the SF-36 pain assessment can be utilised to identify response to treatment to reduce pain in CP [73].

  postoperativer Schmerz,

- **Renal function (population 2):**
  Kidney function in patients who received a renal transplant with ICT can indicate the efficacy of transplant function [68]. Poor functioning of transplanted islet cells can be associated with poor kidney function, as indicated through blood testing such as glomerular filtration rate (GFR) or creatinine levels [68].

  Nierenfunktion

4.1.2 Outcomes safety

The following outcomes were defined as *crucial* to derive a recommendation:

entscheidungsrelevante Sicherheitsendpunkte:

- **Adverse events and complications (all populations):**
  AEs are defined as 'untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment' [74]. AEs have been separated by severity according to the discretion of the individual studies extracted. AEs include those associated with immunosuppression in populations two and three who are required to be on immunosuppressive regimens due to the allogenic nature of relevant ICT therapies. Complications of immunosuppression are also reported for populations two and three within this outcome measure.

unerwünschte Ereignisse (AEs),

- **Mortality (all populations):**
  The survival of patients post-ICT can be related to procedural complications or complications associated with CP or T1D. Both are reported as mortality rates within the included studies.

Mortalität

4.2 Included studies

4.2.1 Included studies effectiveness and safety

Study characteristics and results of included studies are displayed in Table A-1 to Table A-7 and in the evidence profile in Table A-12 to Table A-15.

Chronic pancreatitis

Three case series were included as evidence for the safety and efficacy of ICT for population one (patients with CP who underwent total pancreatectomy) [1-3]. All studies identified were single arm, with two being conducted in the United States (US) and one in the UK in medical centre environments, with population sizes ranging from 60 to 166. No evidence for patients <18 years was identified within literature searches. Follow-up durations ranged from 24-125 months. All ICT was autologous, and all studies investigated the intervention in addition to pancreatectomy.

CP: 3 einarmige Fallserien mit autologer IZT

60-166 Patient:innen

24-125 Monate FU

One study comparing open and laparoscopic ICT with pancreatectomy was not included in this report as it did not meet the PICO criteria [2]. The occurrence of hyperglycaemic events and graft failure were not investigated in any of the included studies and overall complication rates were not identified. Mean and median ages of participants in the studies ranged from 41.1-44.0 years, with the percentage of females ranging from 62-65%. Mean and median BMI of patients within each of the studies ranged from 22.7-26.6 kg/m^2.

Alter: 41-44 Jahre

BMI. 22,7-26,6 kg/m^2

Inclusion criteria, where specified within the studies, included the presence of intractable pain and a diagnosis of CP. One study specified additional physiological outcomes including C-peptide and insulin measurements [3]. One study also grouped patients as 'good', 'partial' and 'poor' responders based on exogenous insulin requirement [1].

Einschlusskriterien

T1D with kidney transplant

T1D + NierenTx + allogene IZT: 1 RCT, 2 NRSI und 3 Fallserien

One RCT, two NRSIs and three single-arm case series were included for the population of T1D patients with severe hypoglycaemia and kidney transplant, typically due to chronic renal failure [4-9]. The populations included within the studies ranged from 23-72 patients, with four studies being conducted in France and two in the US. Follow-up durations ranged from a median of six months to 120 months. All ICTs were allogeneic and involved sourcing islet cells from a deceased donor.

IZT vs. Insulintherapie sowie IZT mit vs. ohne Nierentransplantation

The RCT and one NRSI compared ICT to insulin therapy [4, 8]. The other NRSI compared ICT plus concomitant kidney transplantation, with ICT alone [6]. Two of the single-arm case series had suspected patient overlap, with patients enrolled in the same clinical trial included within the analysis [8, 9].

RCT: IZT + NierenTx vs. Insulintherapie

50 Patient:innen, Ø Alter: 51 Jahre

The median age of participants in the RCT (n=50) was 51 years (41-58), with the median age of ICT participants being 52 (40-57) and the age of the insulin comparator group being 51 (42-58) [4]. Within the study, 57% of participants were female, with 48% and 68% of female participants within the ICT and insulin groups, respectively. Total BMI within the study was 23.7 kg/m^2 (21.9-25.5), with the ICT group having a median BMI of 22.9 (21.9 to 25.5) and the insulin group a BMI of 23·9 kg/m^2 (22.2 to 25.5).

NRSI: IZT allein vs. IZT + NierenTx; 72 Patient:innen, Ø Alter: 48 vs. 52 Jahe

Within the NRSI (n=72) comparing ICT with and without kidney transplant, mean age for the ICT group was 47.8±11.5 and the ICT plus kidney transplant group was 51.8±11.1. In the ICT group, 60% of participants were female; 46% for the ICT plus kidney transplant group. Mean BMI was 24.9± 3.1 kg/m^2 for ICT and 24.6±3.1 for ICT plus kidney transplant.

NRSI: IZT + NierenTx vs. Insulintherapie; 30 Patient:innen, Ø Alter: 43 vs. 40

For patients in the other NRSI (n=30), where ICT patients were compared to those who underwent insulin therapy, mean age for the ICT group was 43.1± 6.2 years and 40.0±7.7 for insulin patients; 54% of participants were female in the ICT group and 71% in the insulin therapy group. Mean BMI was not reported for either group.

3 Fallserien, insgesamt 75 Patient:innen Alter: 43 bis 54 Jahre

Within the remaining three single-arm studies (n=75), mean and median age ranged from 43 to 54 years and the proportion of female patients enrolled ranged from 46% to 52%. Median BMI ranged between 28 and 36.5 kg/m^2.

T1D only

T1D + allogene IZT:

1 NRSI: IZT vs. PankreasTx

2 einarmige Fallserien

One NRSI and two case series were included for the population of T1D patients with severe hypoglycaemia and no chronic renal failure [10-12]. The two included case studies were conducted in the US and Canada, while one NRSI featured pancreas tissue transplant as a comparator and was conducted in Italy. It should be noted that the NRSI had different inclusion criteria for ICT and pancreas transplant. This reflects clinical practice (expert clinical advice) and limits the relevance of this comparison. However, the study has been included in line with the PICO and to inform decision-making. Included population sizes ranged from 36 to 66, with follow-up of <12 months to a median of 41 months. All included studies investigated allogenic ICT involving deceased donors. Across the studies, the only missing outcome of interest was overall complication rates of the procedures, which was unreported within the included studies.

Mean participant age within the NRSI (n=66) was 36±8.6 years for ICT patients and 37±8.4 for pancreas tissue transplant patients; 45.4% of the ICT group and 42.2% of the pancreas transplant group was female. BMI of enrolled patients was not reported.

NRSI:
66 Patient:innen
Ø Alter: 36 Jahre

A median age of 48.4 (26.2-65.5) was reported for one case series (n=48) and a range of 30-59 was reported for the other single-arm study (n=36). One study did not report on sex ratios; 60% of participants in the other study were female. BMI was reported in both studies, with one reporting a mean of 25.1 kg/m^2 (18.9-29.8) and the other a range of 19-25 kg/m^2.

2 Fallserien, insgesamt
84 Patient:innen,
Alter: 30-50 Jahre

The selection criteria expressed within all studies included being >18 years of age, having a diagnosis of diabetes for more than five years with the presence of severe hypoglycaemia, presence of biomarkers indicative of T1D and eligible for transplantation considering comorbidities and health status.

Einschlusskriterien der Studien

4.3 Results

4.3.1 Chronic pancreatitis

Function[4]

Glycaemic control

HbA1c

Two case series reported increased and stable HbA1c levels within the CP sub-population following ICT [1, 3]. One study reported that compared to baseline (6.0%; standard deviation [SD] 1.1%), ICT patients maintained an increased percentage of HbA1c at one year (7.3%; SD 2.0%), two years (7.3%; SD 2.4%) and three years (7.0%; SD 1.4%) post-intervention, suggesting slightly poorer glycaemic control than pre-pancreatectomy and ICT, although the statistical and clinical significance of such findings was not reported [3]. Another case series also identified higher HbA1c levels for up to ten years postoperatively in ICT patients who had been identified as good responders in regard to predefined criteria, where patients were insulin independent for the first five years after total pancreatectomy and ICT [1]. Patients identified as partial or poor responders (varying levels of exogenous insulin required in the years following ICT) had significantly greater HbA1c compared to good responders (two-way ANOVA $p<0.0003$ and $p<0.0001$, respectively) after ICT, indicating that good responders had greater glycaemic control and graft function [1].

CP mit autologer IZT:

verbesserte HBA1c-Werte über mehrere Jahre in 2 Fallserien

[4] This section addresses the following assessment elements:
D0011 – What is the effect of the technology on patients' body functions?
D0005 – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006 – How does the technology affect progression (or recurrence) of the disease or health condition?

C-peptide secretion

konstante C-Peptid-Werte über 3-10 Jahre in 2 Fallserien

Two case series reported maintained C-peptide levels following pancreatectomy and ICT [1, 3]. Coluzzi et al. reported consistent mean C-peptide levels from baseline (1.8±1.3 ng/dL) to one year (1.2±1.2 ng/dL), two years (1.4±1.5 ng/dL) and three years (1.1±1.3 ng/dL) postoperatively. C-peptide levels also remained stable in 'good' ICT responders for up to ten years post-ICT in a separate study [1]. When combined with glucose stimulation via OGTT, patients with partial and poor responses to ICT still experienced increases in C-peptide levels within 120 minutes post-assessment, indicating graft activity [1].

Fasting blood glucose

stabile glykämische Kontrolle bis 3 Jahre FU in 1 Fallserie

One single arm study reported fasting blood glucose levels, which indicated ongoing stable glycaemic control post-ICT [3]. Compared to baseline (102±29 mg/dL), fasting blood glucose levels were maintained at one year (152±94 mg/dL), two years (151±65 mg/dL) and three years (124±5 mg/dL) years post-ICT [3].

Hypoglycaemia

No evidence was found to answer this research question.

Insulin

Insulin independence

Insulinunabhängigkeit nach 2 Jahren FU variiert stark in 2 Fallserien: 19 % vs. 73 %

All three included case series reported varying rates of insulin independence post-ICT [1-3]. In one study, 14 of 61 ICT patients reached insulin independence at one month post-transplant, with 19% of patients reaching insulin independence up to 24 months post-intervention [2]. Good responders to ICT reported insulin independence of 29.4% (5 of 17 patients) at five years post-transplant and 17.6% (3 of 17 patients) at ten years post-transplant [1]. One third of partial ICT responders (33%; 2 out of 6 patients) also had a period of insulin independence for six months post-ICT [1]. The study by Coluzzi et al. identified insulin dependence rates of 78%, 73% and 71% at one, two and three years, respectively, post-ICT [3].

Exogenous insulin requirement

unterschiedlicher Insulinbedarf nach Transplantation in 3 Fallserien

Insulin requirements for patients were reported in all three included studies [1-3].One study reported that 27% of participants required <10 units of insulin, 23% required 11-25 units and 31% of participants required >25 units of insulin [2]. Another study separated patients into good responders to ICT (5 of 17 patients) requiring no insulin for five years post-transplant and <10 units/day up to ten years post-TPIAT, partial responders (6 of 17 patients) who required <20 units/day post-ICT, and poor responders who required >20 units/day (6 of 17 patients) post-transplant [1]. Compared to baseline (mean 2.2±8.0 units/day), mean insulin requirements increased post-ICT to 14.7±15.0 units/day at one year, 15.5±15.9 units/day at two years and 14.4±17.5 units/day at three years post-ICT [3].

Graft failure

Transplantatversagen: keine Evidenz

No evidence was found to answer this research question.

Pain

Pain score

Schmerzreduktion in 2 Fallserien

Two case series reported pain after ICT and pancreatectomy in CP patients [2, 3]. One study conducted an SF-36 pain assessment up to one year post-ICT [2]. Compared to baseline (mean 25.2±19.3), mean pain scores were found to improve following the intervention at one month (34.7±18.8), six months (52.0±29.7) and twelve months (57.4±25.7) post-ICT (statistical significance not reported) [2]. A visual analogue assessment (VAS) pain assessment was conducted in another study, identifying a significant reduction in pain post-ICT and pancreatectomy from baseline (5.7±2.1) to three years (1.9±2.6) post-intervention ($p<0.001$) [3].

Analgesic use

weniger/keine Schmerzmitteleinnahme nach IZT in 2 Fallserien

Use of analgesics and pain therapeutics was reported in two single-arm studies, indicating a positive response to ICT with pancreatectomy [2, 3]. In one study, 71% of ICT patients reported no longer requiring analgesics to manage pain [2]. The morphine equivalent dose was significantly reduced ($p<0.001$) in ICT patients, from 118±137 mg/dL at baseline to 35±65 mg/dL at three years post-intervention [3].

Quality of Life[5]

Lebensqualität klinisch signifikant verbessert in einzelne Domänen des EORTC QLQ-30 (z. B. körperliche Funktion) & EORTC QLQ-PAN26 (z. B. Schmerzen) in 1 Fallserie

One case series reported on the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-30) to assess patient function and ongoing symptoms of treatments following ICT and pancreatectomy in CP patients [3]. At a two-year follow-up, patients noted improved global health QoL (34.84±23.79 vs 55.38±27.01; $p<0.001$), physical functioning (62.82±24.14 vs 76.13±21.83; $p<0.001$), role functioning (37.21±30.72 vs 60.75±38.38; $p<0.001$), emotional functioning (42.17±26.36 vs 58.06±30.99; $p<0.001$), cognitive functioning (55.26±29.94 vs 65.59±27.87; $p=0.007$) and social functioning (30.32±32.65 vs 52.69±72.41; $p<0.001$), which were determined to be clinically significant improvements in the functional domains compared to baseline measurements (≥10 points) [3]. Improvements were also observed within symptom domains of the assessment, including fatigue (72.41±26.39 vs 45.16±24.83; $p<0.001$), nausea and vomiting (57.90±33.08 vs 35.48±35.42; $p<0.001$), pain (72.41±26.39 vs 45.16±24.83; $p<0.001$), insomnia (75.00±30.10 vs 48.39±32.02; $p<0.001$), appetite loss (66.95±34.19 vs 29.03±31.90; $p=0.001$) and constipation (50.00±37.94 vs 23.66±27.48; $p<0.001$), with such findings being determined as clinically significant (defined as an improvement and score reduction ≥20 points) [3]. EORTC QLQ-PAN26 symptom scales revealed statistically improved changes in all domains, including pancreatic pain (73.41±24.95 vs 42.74±23.25; $p<0.001$), bloating (66.67±30.46 vs 46.24±32.97; $p<0.001$), digestive symptoms (77.97±28.66 vs 52.15±34.09; $p<0.001$), taste (37.07±33.99 vs 20.43±28.12; $p=0.009$), indigestion (50.86±36.11 vs 26.88±29.08; $p=0.001$), weight loss (66.67±30.46 vs 46.24±32.97; $p<0.001$), body image (33.05±22.84 vs 20.97±18.24; $p=0.003$) and future worries (54.89±37.37 vs 43.01±30.05; $p=0.009$), with clinically significant improvements in all areas excluding flatulence, hepatic symptoms,

[5] This section addresses the following assessment elements:
D0012 – What is the effect of the technology on generic health-related quality of life?
D0013 – What is the effect of the technology on disease-specific quality of life?

and the trouble with side effects domain (p>0.05) [3]. Functional assessment using EORTC QLQ-PAN26 also revealed significant improvements in satisfaction with healthcare (18.25±23.97 vs 22.58±23.78; p=0.004) and sexuality (78.26±24.50 vs 57.53±30.98; p<0.001) [3].

Patient safety

Complications and adverse events

Overall complication rate

No included studies reported overall procedure-related complication rates.

Gesamtkomplikationsrate: keine Evidenz

Major and minor adverse events

No included studies reported AEs.

(S)AEs: keine Evidenz

Length of hospital stay

Length of stay was reported in one case series [2]. Overall, patients remained in hospital for a mean of 12.4±4.4 days [2].

Ø Tage im Krankenhaus: 12

Mortality[6]

Survival rate

Three case series reported patient survival [1-3]. In one study, patient survival was 100% at 30 days post-transplant. In a separate study, 16 patients had died by the conclusion of the study period (two years) due to alcohol consumption, heart disease, diabetes complications and unknown reasons that may or may not be related to ICT and pancreatectomy. A separate study found that two patients died at one year, six patients died at two years and nine patients had died by three-years post-ICT and pancreatectomy; however, the causes of these deaths were not reported.

keine Todesfälle bis 30 Tage FU in 1 Fallserie;
16 Todesfälle bis 2 Jahre FU in 1 Fallserie;
17 Todesfälle bis 3 Jahre FU in 1 Fallserie

Procedure-related mortality

Two case series reported no deaths associated with the ICT and pancreatectomy procedure for CP patients [1, 2].

keine Todesfälle durch IZT in 2 Fallserien

[6] **D0001** – What is the expected beneficial effect of the technology on mortality?

4.3.2 T1D with Kidney Transplant

ICT vs insulin therapy

Function[7]

Glycaemic control

HbA1c and β score

The included RCT reported on several measures of HbA1c following ICT [4]. Compared to baseline, at six months post-intervention commencement, the ICT and kidney transplant group had a significantly higher median modified β-score (0, interquartile range [IQR] 0-2 vs 6, 5-7; p<0·0001) with 16 of 25 patients (64%; 95% confidence interval [CI] 43-82) having a modified β-score of six or higher [4]. The insulin therapy group also experienced improvements in β-score from baseline (0, IQR 0-1 vs 1.5, 0.0-2.0; p=0.0091), with zero patients of the 22 enrolled (0%, IQR 0-15) having a modified β-score of six or higher [4]. HbA1c levels assessed between groups revealed significant differences in HbA1c levels of 5.6% (38 millimoles per mole [mmol/mol]) for ICT patients vs 8.2% (66 mmol/mol) for insulin therapy patients at six months post-intervention (p<0.0001), indicating improved glycaemic control [4]. In addition, 21 ICT patients (84%; 95% CI 64-96]) versus zero insulin therapy patients (0%; 95% CI 0-15) had HbA1c <7%, indicating glycaemic control, favouring ICT for T1D management (p<0.0001).

T1D + IZT+ NierenTx vs. Insulintherapie

HBA1c: signifikant niedrigere Werte bei IZT vs. Insulintherapie in 1 RCT

HbA1c <7 % in 1 RCT: 84 % IZT, 0 % Insulintherapie

An NRSI comparing T1D ICT patients with those undergoing insulin therapy revealed that significant decreases in HbA1c from baseline were observed in ICT at one year (8.2±1.1 vs 6.1±0.7) and two years (8.2±1.1 vs 6.4±1.0) post-transplant, and at one year (8.4±1.8 vs 7.9±1.0) and two years (8.4±1.8 vs 7.5±0.8) after the commencement of insulin therapy (p<0.001 and p<0.01 for ICT and insulin patients, respectively) [8]. At three years post-intervention, significant differences from baseline were observed in ICT patients (8.2± 1.1 vs 6.6±1.1; p<0.01), but not in the insulin therapy group (8.4±1.8 vs 8.1±1.3; p=NS) [8]. Between-groups analysis revealed significant differences between HbA1c levels at one year (6.1±0.7 vs 7.9±1.0; p<0.0001), two years (6.4±1.0 vs 7.5±0.8; p<0.01) and three years (6.6±1.1 vs 8.1±1.3; p<0.01) post-trial, indicating improved glycaemic control within the ICT group [8].

HBA1c: signifikant bessere Werte nach IZT bis 3 Jahre FU in 1 NRSI

C-peptide secretion

The included RCT and NRSI for this comparison did not report C-peptide.

C-Peptid: keine Evidenz

Fasting blood glucose

As reported in one RCT, there was no significant difference (p=0.92) in fasting glucose levels between ICT patients and those undergoing insulin therapy (5.9 median mmol/L, IQR 5.2-6.7) vs (5.7 median mmol/L, IQR 4.9-10.9) [4].

Nüchternblutzucker: keine signifikanten Unterschiede in 1 RCT

[7] This section addresses the following assessment elements:
D0011 – What is the effect of the technology on patients' body functions?
D0005 – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006 – How does the technology affect progression (or recurrence) of the disease or health condition?

One NRSI comparing ICT patients and those undergoing insulin therapy reported significant decreases in fasting blood glucose levels from baseline to one year (12.2±3.0 mmol/L vs 6.6±1.1mmol/l; p<0.001), two years (12.2± 3.0 mmol/L vs 6.8±1.3 mmol/L; p<0.001) and three years' post-transplant (12.2±3.0 mmol/L vs 7.1±1.6 mmol/L; p<0.01)[58]. No significant differences in fasting blood glucose were identified in the insulin therapy group from baseline at one year (9.3±3.1 vs 8.8±2.0 mmol/L), two years (9.3±3.1 vs 8.7±2.6 mmol/L) and three years (9.3±3.1 vs 9.0±1.5 mmol/L) follow-up [58]. There were significant differences for fasting blood glucose of ICT patients compared with those undergoing insulin therapy at one year (6.6±1.1 mmol/L ± 8.8±2.0 mmol/L; p<0.05), two years (6.8±1.3 mmol/L vs 8.7±2.6 mmol/L; p<0.05) and three years (7.1±1.6 mmol/L vs 9.0±1.5 mmol/L; p<0.05) post-intervention.

signifikante Reduktion nach IZT vs. Insulintherapie in 1 NRSI

Hypoglycaemia

In the included RCT, a significant difference in the number of severe hypoglycaemic events each year was identified between ICT patients and insulin therapy patients (0 events per year vs 2 events IQR 0-4; p<0.0001), in favour of ICT [4]. In addition, 92% of ICT patients (95% CI 74-99) and 36% of insulin therapy patients (95% CI 17-59) were free of severe hypoglycaemic events at one year post-treatment commencement, with ICT identified as significantly more effective in reducing hypoglycaemic events (p<0.0001) [4].

keine Hypoglykämien nach 1 Jahr FU in 1 RCT:

IZT: 92 %
Insulintherapie: 36 %

An NRSI comparing patients who underwent ICT with those provided insulin therapy found significant reductions in the number of hypoglycaemic events per week in ICT patients at one year (2.6±2.1 vs 0.3±0.5; p<0.05), two years (2.6±2.1 vs 0.2±0.5; p<0.001) and three years (2.6±2.1 vs 0.7±1.1; p<0.01) post-study commencement [8]. No significant differences in the number of hypoglycaemic events were observed at one year (2.9±2.2 vs 1.6±1.6), two years (2.9±2.2 vs 1.5±1.2) and three years (2.9±2.2 vs 1.7±1.8) post therapy commencement [8]. There was a significant improvement in the number of hypoglycaemic events per week in the ICT group compared with the insulin therapy group at one year (0.3±0.5 vs 0.6±1.6; p<0.01) and two years (0.2±0.5 vs 1.5±1.2; p<0.01), but not at three years post-therapy (0.7±1.1 vs 1.7±1.8; p>0.05) [8].

signifikant weniger hypoglykämische Events pro Woche nach IZT vs. Insulintherapie in 1 NRSI

Insulin

Insulin independence

In the included RCT, 27 of 49 (59%, IQR 43-73) ICT recipients were insulin independent at twelve months post-transplantation (p<0.0001 vs baseline) [4]. Assessment of insulin independence within the insulin therapy group was not possible due to the nature of the intervention [4].

Insulinunabhängigkeit 1 Jahr nach IZT in 1 RCT: 59 %

An NRSI comparing ICT with insulin therapy found that at two years follow-up, 6 of 13 ICT patients had achieved insulin independence, while at three years post-transplant, 7 of 13 patients had achieved independence [8].

in 1 NRSI:
2 Jahre FU: 6/13
3 Jahre FU: 7/13

Exogenous insulin requirement

The RCT identified for this population did not report exogenous insulin requirements post-intervention for ICT or the insulin therapy comparator.

Insulin: keine Evidenz aus 1 RCT

An NRSI investigating the difference in insulin requirements between ICT and insulin therapy T1D patients, compared to baseline measures, found significant reductions in the amount of insulin required for ICT patients at one, two and three years' post-transplant (all p<0.001), with no significant differ-

exogenes Insulin: signifikant weniger bei IZT vs. Insulintherapie in 1 NRSI

ences in insulin requirement observed in insulin therapy patients for the same timeframes [8]. There were significant differences in the required amounts of insulin between ICT and insulin therapy participants (p<0.0001) [8].

Islet cell graft failure

The RCT showed that 93% of ICT patients (43 of 46 patients; IQR 82-99) had a functioning islet graft at 1-year post-transplantation, as assessed by HbA1c levels [4].

Inseltransplantat: 93 % funktionsfähig nach 1 Jahr FU in 1 RCT

Renal function

Kidney/renal allograft function

Improvements in renal function were reported in the included RCT for T1D patients with kidney transplantation [4]. Compared to baseline, at twelve months post-intervention, estimated glomerular filtration rate (eGFR) was 90.5 ml/min (IQR 76.6-94) vs 71.8 ml/min (IQR 59-89; p=0.0008) for ICT, and 63 ml/min (IQR 55-71) vs 57 ml/min (IQR 45.5-65.1; p=0.014) for insulin therapy [4]. No inter-group comparison was reported.

verbesserte Nierenfunktionswerte nach IZT in 1 RCT

Diabetes complications

No evidence was found to answer this research question.

sekundäre Diabeteskomplikationen: keine Evidenz

Quality of Life[8]

One RCT comparing ICT and kidney transplant with insulin therapy was identified [4]. The SF-36 functional assessment identified significant improvements in general health perceptions (p=0.008) and health transition (p<0.001) at 6 months post-transplant For ICT patients compared with insulin therapy patients, no differences were reported in other domains [4].

Lebensqualität in 1 RCT: signifikante Verbesserung bei IZT vs. Insulintherapie in 2 Domänen des SF-36

Patient safety[9]

Complications and adverse events

Overall complication rate

One RCT reported procedure-related complications in 19.1% of ICT patients [4]. Complications were not reported for the insulin-only group due to the non-invasive nature of the approach [4]. Procedural AEs that occurred within six months included post-procedural haemorrhage (2.1%), hepatic haematoma (2.1%), traumatic haemothorax (2.1%), postoperative renal failure (2.1%), post-procedural haematoma (2.1%), arterial injury (2.1%), subcutaneous haematoma (2.1%) and peritoneal haemorrhage (2.1%) [4].

verfahrensbedingte Komplikationen bei IZT in 1 RCT: 19,1 %

[8] This section addresses the following assessment elements:
D0012 – What is the effect of the technology on generic health-related quality of life?
D0013 – What is the effect of the technology on disease-specific quality of life?

[9] This section addresses the following assessment elements:
C0008 – How safe is the technology in comparison to the comparator(s)?
C0004 – How does the frequency or severity of harms change over time or in different settings?

Major and minor adverse events

Serious AEs (SAEs) were reported in one RCT for all patients undergoing ICT and for all patients who underwent crossover to the ICT group following insulin therapy [4]. In the insulin group, the only recorded SAE was infection in one patient (5%) [4]. In all patients who underwent ICT, reported AEs included infections and infestations (42.6%) including acute pyelonephritis (4.3%), gastrointestinal disorders (38.3%) including the onset of vomiting (12.8%) and diarrhoea (8.5%), blood and lymphatic disorders (34%) including leukopenia (6.4%) and neutropenia (10.6%), onset of cardiac disorders including a case of fatal cardiac arrest (2.1%), myocarditis (2.1%), transient cardiac arrest (2.1%), atrial fibrillation (2.1%) and paroxysmal tachycardia (2.1%), general disorders and administration site conditions (12.8%), immune disorders (12.8%) including transplant rejections (8.5%), metabolism and nutrition disorders (12.8%), musculoskeletal and connective tissue disorders (10.6%), nervous system disorders (17%), renal and urinary disorders (12.8%), and respiratory, thoracic and mediastinal disorders (8.5%) [4].

zahlreiche SAEs bei IZT in 1 RCT

häufigste Komplikationen: Infektionen und Infektionskrankheiten (42,6 %), gastrointestinale Störungen (38,3 %), Blut- und Lymphgefäß-erkrankungen (34 %)

One NRSI, comparing AEs in patients receiving ICT plus insulin therapy, identified 17 grade three SAEs within one year of therapy in the total population of 13 patients, including events such as elevated liver enzymes (1), neutropenia (4), dysautonomia decompensation (2) and proteinuria (1); and one grade 4 SAE (choleperitonitis) [8]. In the control group (insulin alone, total population 17 patients), ten grade three SAEs were reported including glucose imbalance (4), abdominal pain (5) and pump dysfunction (3); one grade four SAE was reported (infection/pump explantation) [8]. Grade three AEs were not reported at two years post-intervention, and no grade four SAEs were identified at two years post-transplant [8].

Grad 3 SAEs in 1 NRSI:

IZT: 17 in 13 Pat.

Insulintherapie: 10 in 17 Pat.

Length of hospital stay

No evidence was found to answer this research question.

Länge der Hospitalisierung: keine Evidenz

Mortality[10]

Survival rate

No evidence was found to answer this research question.

Überlebensrate: keine Evidenz

Procedure-related mortality

No evidence was found to answer this research question.

verfahrensbedingte Mortalität: keine Evidenz

[10] **D0001** – What is the expected beneficial effect of the technology on mortality?

ICT alone vs ICT with kidney transplant

Function[11]

Glycaemic control

HbA1c and β score

NRSI: IZT + NierenTx vs. IZT allein

HBA1c < 6,5 % in 1 NRSI: bei 17 % mit NierenTx nach 7 Jahren FU

One NRSI compared patients undergoing ICT alone versus those undergoing ICT with a kidney transplant. Rickels et al. found that 49% of ICT patients maintained levels of HBA1C <7.0% but no patients had levels <6.5% after 8.3 years of follow-up [5]. In contrast, 35% of ICT plus kidney transplant patients maintained an HbA1c level of <7.0% in the same timeframe as ICT patients alone, with a significant difference noted between the groups (p=0.0017) [5]. However, 17% of ICT plus kidney transplant patients maintained an HbA1c level <6.5% at maximum follow-up of 7.3 years, with a significant improvement for the ICT plus kidney transplant group compared with ICT alone (p<0.0001) [5].

C-peptide secretion

C-Peptid-Level-Anstieg in beiden Gruppen in 1 NRSI

One NRSI reported C-peptide levels for ICT with and without kidney transplantation [5]. For ICT alone, mean fasting C-peptide levels increased from undetectable levels to a peak of 1.7 ng/mL at one year post-transplant, then gradually decreased to 1.3 ng/mL at three years, 1.2ng/mL at median follow-up of 5.6 years and 1.0 at eight years [5]. In ICT plus kidney transplant patients, mean fasting C-peptide increased from undetectable levels at baseline to a peak of 2.0ng/mL, then fell to 1.5ng/mL at the median follow-up of 3.3 years and dropped to 0.7 ng/mL at 7.1 years [5]. The NRSI did not compare C-peptide levels between groups.

Fasting blood glucose

Nüchternblutglukose: keine Evidenz

No evidence was found to answer this research question.

Hypoglycaemia

keine hypoglykämischen Events während FU in 1 NRSI

One comparative NRSI reported hypoglycaemic events in ICT alone and ICT plus kidney transplant patients [5]. There was a total of twelve hypoglycaemic events across five patients (7%), three patients with ICT alone and two with ICT plus kidney transplant [5]. No glycaemic events in patients were reported across all follow-up times [5].

Insulin

Insulin independence

Insulinunabhängigkeit nach 8 Jahren in 1 NRSI: IZT allein: 54 %, IZT + NierenTx: 63 %

One NRSI comparing ICT alone and ICT plus kidney transplant [5] showed that 37 of 48 ICT-alone patients and 16 of 24 ICT plus kidney transplant patients achieved a period of insulin independence, with HbA1c maintained at <7.0% (not-significant between groups, p value not reported) [5]. Across all participants, 20 patients with one islet infusion (37.66%), 20 patients with two islet infusions (56.66%) and three patients with three infusions (5.66%)

[11] This section addresses the following assessment elements:
D0011 – What is the effect of the technology on patients' body functions?
D0005 – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006 – How does the technology affect progression (or recurrence) of the disease or health condition?

achieved insulin independence [5]. It was also reported that 20 of 37 ICT-alone patients and ten of 16 ICT plus kidney transplant patients maintained insulin independence for a median follow-up of eight years, with no significant differences identified between the groups [5].

Exogenous insulin requirement

In one comparative study there was a median reduction in insulin dose of 54% in ICT plus kidney transplant patients (81% decrease to 34% increase) [5].

exogenes Insulin in 1 NRSI um 54 % reduziert bei Pat. mit NierenTx

Islet cell graft failure

One NRSI investigating ICT alone and ICT plus kidney transplant reported on long-term islet graft survival [5]. At maximum follow-up of 8.3 years, 56% of islet grafts within ICT-alone patients were identified as functional; 49% of ICT plus kidney transplant patients had a functioning graft at maximum follow-up of 7.3 years [5].

Inselzelltransplantat: ca. 50 % funktionsfähig nach 7 Jahre FU in 1 NRSI

Renal function

Kidney/renal allograft function

One NRSI study of ICT-alone patients and ICT plus kidney transplant patients reported eGFR [5]. It was identified that in ICT-alone patients, eGFR declined by 6.9mL/min/1.73 m^2 (millilitres of cleansed blood per minute per body surface) within one year post-transplant compared to ICT plus kidney transplantation, which showed a decrease in eGFR by 0.7 mL/min/1.73 m^2, indicating that kidney function was maintained more effectively by ICT plus kidney transplant compared to ICT [5].

bessere Nierenfunktion bei zusätzlicher NierenTx in 1 NRSI

Diabetes complications

Results from one NRSI study showed no increased risk of development of cardiovascular risk factors after ICT, as assessed by patient carotid intimal thickness [5]. No other reported secondary diabetes complication was identified in any other included study.

kein höheres Risiko für KHK in 1 NRSI

Quality of Life[12]

No evidence was found to answer this research question.

Lebensqualität: keine Evidenz

Patient safety[13]

Complications and adverse events

Overall complication rate

No evidence was found to answer this research question.

Gesamtkomplikationsrate: keine Evidenz

[12] This section addresses the following assessment elements:
D0012 – What is the effect of the technology on generic health-related quality of life?
D0013 – What is the effect of the technology on disease-specific quality of life?

[13] This section addresses the following assessment elements:
C0008 – How safe is the technology in comparison to the comparator(s)?
C0004 – How does the frequency or severity of harms change over time or in different settings?

Major and minor adverse events

One NRSI identified SAEs in ICT-alone and ICT plus kidney transplant patients [5]. An analysis of separate SAEs was not provided by the study authors. A total of 104 SAEs were reported across both cohorts, with the ICT-alone group reporting 71 SAEs in 27 of 48 subjects, including 36 SAEs in the primary study and 35 in long-term follow-up [5]. In the ICT plus kidney transplant group, 33 SAEs in 15 of 24 subjects were reported, 29 SAEs in the primary study and four in long-term follow-up [5]. Within the ICT-alone group, an additional 37 SAEs unrelated to the therapy were identified, compared to 15 in the ICT and kidney transplant group.

SAEs: 104 in 1 NRSI

IZT allein: 71 in 27/48 Patient:innen

IZT + NierenTx: 33 in 15/24 Patient:innen

Length of hospital stay

No evidence was found to answer this research question.

Krankenhausaufenthalt: keine Evidenz

Mortality[14]

Survival rate

One NRSI that produced single-arm data reported a 100% survival rate for all patients within both studies, up to three years follow-up in both cases [5, 7].

100 % Überlebensrate in 1 NRSI

Procedure-related mortality

No evidence was found to answer this research question.

behandlungsbedingte Mortalität: keine Evidenz

ICT single-arm

Function[15]

Glycaemic control

HbA1c and β score

Three case series provided single-arm evidence for changes in HbA1c levels following ICT [6, 7, 9]. One study showed median HbA1c levels significantly decreased at six months (6.0%, IQR 5.7-6.4; p<0.01) and twelve months (6.7%, IQR 5.9-7.7; p<0.01) compared to baseline (8.37%, IQR 3-9), indicating efficacy of the transplanted cells [9]. In a separate study, HbA1c levels also significantly decreased at one year (6.0% IQR 5.3-6.4; p< 0.001), two years (6.3% IQR 5.5-6.7; p=0.002) and three years (6.3% IQR 5.5-6.9; p< 0.001) post-transplant [7]. Similar reductions were also reflected in another study, showing significant reductions compared with baseline HbA1c in ICT patients at one (5.9% IQR 5.5-6.7; p<0.0001), five (6.9% IQR 6.1-7.5; p<0.0001) and ten years (6.7% IQR 6.1-8; p=0.0009) post-transplant, suggesting continued efficacy of ICT over long periods.

3 einarmige Fallserien zu IZT + NierenTx:

HBA1c: signifikante Reduktion über mehrere Jahre in 3 Fallserien

[14] **D0001** – What is the expected beneficial effect of the technology on mortality?

[15] This section addresses the following assessment elements:
D0011 – What is the effect of the technology on patients' body functions?
D0005 – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006 – How does the technology affect progression (or recurrence) of the disease or health condition?

C-peptide secretion

C-Peptid-Level in 1 Fallserie deutlich höher als vor IZT

One case series reported C-peptide levels in ICT recipients [7]. All patients had non-detectable C-peptide levels prior to transplantation, which increased to 1.8 ng/mL (IQR 1.6-2.5) one year, 1.8ng/mL (IQR 1.5-2.1) at two years, and 1.3 ng/mL (IQR 0.8-1.6) at three years post-ICT [5]. Mixed meal tolerance testing at 60 and 90 minutes post-meal also revealed significantly increased C-peptide readings at one, two and three years in both test timeframes (60 minutes post ingestion: one year 5.2 ng/mL [IQR 3.6-7.7], two year: 4.4 ng/mL [IQR 2.7-5.1], three year: 4.4 ng/mL [IQR 1.2-8.2]) ($p \leq 0.001$ for all comparisons against baseline), (90 minutes post-meal ingestion: one year: 5.5 ng/mL [IQR 4.1-6.7], two year: 4.0 ng/mL [IQR 3.6-6.8], three year: 4.4 ng/mL [IQR 1.3-7.2]) ($p<0.001$ for all comparisons against baseline) [7].

Fasting blood glucose

Nüchternblutzucker signifikant reduziert nach 1 Jahr FU in 2 Fallserien

In two single-arm studies, fasting blood glucose was reported in ICT patients. In one study, significant reductions in fasting blood glucose were identified at one year post-ICT (109.0 mg/dL, IQR 101.0-115; $p=0.036$), however these reductions did not maintain statistical significance at two years (112.0mg/dL, IQR 99.5-127.0; $p=0.175$) and three years (111.0 mg/dL, IQR 99.00-127.0; $p=0.334$) post-transplant [7]. In a long term study significant reductions in blood glucose compared to patient baselines were identified at one (112 mg/dL, IQR 102-133; $p<0.0001$), five (126 md/dL, 110-144; $p<0.0001$), and ten years (118 mg/dL, IQR 113-154; $p=0.0007$) [6].

Hypoglycaemia

Hypoglykämiezeit und Anzahl von Events in 3 Fallserien reduziert

Hypoglycaemia was reported in three single-arm studies investigating patients who underwent ICT with kidney transplantation [6, 9]. In one study, the percentage of time in hypoglycaemia following ICT was compared to baseline, revealing a significant decrease in the amount of time spent in hypoglycaemia at six months (0%, IQR 0 -3.5; $p<0.05$) and twelve months (0%,IQR 0-2; $p<0.05$) post-transplant [9]. Another study revealed that severe hypoglycaemic events ceased in ICT patients at one (79.2%) ($p=0.003$), two (75.0%) ($p=0.011$) and three years (62.5%), ($p=0.154$). In a long-term study, no hypoglycaemic events were reported in ICT patients from one to ten years post-transplant (0 events total) ($p<0.0001$) [6].

Insulin

Insulin independence

Insulinunabhängigkeit nach 3 Jahren in 1 Fallserie: 17 %

One case series reported insulin independence in ICT and kidney transplant patients [7]. Insulin independence was reached in 37.5% of patients at one year ($p=0.036$ compared with baseline), 29.2% of patients at two years ($p=0.189$) and 16.7% of patients at three years ($p=0.736$) post-transplant [7].

Exogenous insulin requirement

exogener Insulinbedarf: signifikante Reduktion in 2 Fallserien

Two single-arm studies reported on exogenous insulin post-ICT transplant [7]. One study identified significant reductions in the amount of required insulin post-transplant at baseline (0.50 units/kg, IQR 0.39-0.58) to one (0.0 units/kg, IQR 0.0-0.01; $p<0.001$), two (0.00 units/kg, IQR 0.0-0.22; $p<0.001$) and three years (0.00 units/kg, IQR 0.00-0.26; $p=0.002$) post-transplant [7]. Long-term reductions in exogenous insulin requirements were also identified at one (0, IQR0-0.04, five (0 [-0-0.36]) and ten years (0.28, IQR 0-0.43) post-ICT ($p<0.0001$) [6].

Islet cell graft failure

One case series found that six of 28 patients experienced graft failure [6]. A Kaplan-Meier estimate of graft survival in the entire study group revealed an estimated survival rate of 82% at five years post-transplant (95% CI 62-92) and 78% (95% CI 57-89) at ten years post-transplant [6].

Transplantatversagen in 1 Fallserie: 6/28

Renal function

Kidney/renal allograft function

Two single-arm studies reported eGFR rate [6, 7]. A significant decline in kidney function was identified by a significantly lower eGFR at 75 days post-ICT (70 mL/min/1.73m^2, IQR 52-83) compared to baseline (82 mL/min/1.73 m^2, IQR 56-86; p<0.001); however, this was not significant at one (p=0.568), two (p=0.268) and three years (p=0.583) post-transplant [7]. A non-significant difference in eGFR was identified at one (68 mL/min/1.73 m^2, IQR 55-81), five (64 mL/min/1.73 m^2, IQR 51-80) and ten years (54 mL/min/1.73 m^2, IQR 43-91), with gradual but non-significant differences in filtration noted within this time [6].

Nierenfunktion: Abnahme über 10 Jahre in 2 Fallserien

Immunosuppression

No evidence was found to answer this research question.

Immunosuppression: keine Evidenz

Diabetes complications

No evidence was found to answer this research question.

sekundäre Diabeteskomplikationen: keine Evidenz

Quality of Life[16]

One case series reported QoL outcomes of patients with ICT and kidney transplant [7]. One study completed several assessments including the diabetes distress core (DDS), indicating significant improvements compared to baseline at 75 days (8, IQR 1.7-2.8; p=0.002), one year (1.5, IQR 1.3-1.9; p=0.006), two years (1.6, IQR 1.2-1.8; p=0.019) and three years (1.7, IQR 1.1-2.4; p=0.008) post-transplant, showing improvements in diabetes symptoms and psychosocial wellbeing of patients as indicated by reduced distress scores over time [7]. Within the same study, patients also completed the Hypoglycaemia Fear Score, which identified significant reductions in patient anxiety towards hypoglycaemic events in patients at 75 days (1.3, IQR 0.96-1.9; p<0.001) and one year (0.74, IQR 0.0-1.74; p=0.002) post-transplant compared to baseline (2.0, IQR 1.7-2.4); however, not at two (0.41, IQR 0.0-1.6; p=0.039) and three years (0.6, IQR 0.0-1.7; p=0.047) post-transplant [7]. The EuroQOL Visual Analog Scale was utilised to assess overall health state, revealing significant improvements from baseline at one year post-transplant (79.0, IQR 75.0-82.0; p< 0.001), but not at two (80.0, IQR 74.0-85.0; p=0.095) or three years (78.0, IQR 70.0-85.5; p=0.033) post-transplant [7].

Diabetes-Belastung: signifikante Verbesserung bis 3 Jahre nach IZT in 1 Fallserie

EuroQOL-Skala zeigt verbesserten Gesundheitszustand nach 1 Jahr in 1 Fallserie

[16] This section addresses the following assessment elements:
D0012 – What is the effect of the technology on generic health-related quality of life?
D0013 – What is the effect of the technology on disease-specific quality of life?

Patient safety[17]

Complications and adverse events

Overall complication rate

No evidence was found to answer this research question.

Gesamtkomplikationsrate: keine Evidenz

Major and minor adverse events

One case series reported complications and AEs associated with ICT therapy [6]. A total of 17 SAEs were reported in ICT patients at one year post-intervention, including eleven procedure-related events, five events immunosuppression-related events including infections and haematological disorder, and one related to diabetes complications [6]. Between one to ten years post-transplant, 19 SAEs were reported, with eight associated with immunosuppression, including infections and cancer onset, and eleven associated with diabetes complications, including myocardial infarct and pulmonary oedema [6].

SAEs in 1 Fallserie:

bis 1 Jahr FU: 17
1-10 Jahre FU: 19

Length of hospital stay

No evidence was found to answer this research question.

Krankenhausaufenthalt: keine Evidenz

Mortality[18]

Survival rate

One case series reported 100% survival rate for all patients in both studies, up to three years follow-up in both cases [5, 7].

100 % Überlebensrate in 1 Fallserie

Procedure-related mortality

No evidence was found to answer this research question.

behandlungsbedingte Mortalität: keine Evidenz

4.3.3 T1D without kidney transplant

ICT vs pancreas transplant[19]

Glycaemic control

HbA1c

No evidence was found to answer this research question.

HBA1c: keine Evidenz

C-peptide secretion

No evidence was found to answer this research question.

C-Peptid: keine Evidenz

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[17] This section addresses the following assessment elements:
C0008 – How safe is the technology in comparison to the comparator(s)?
C0004 – How does the frequency or severity of harms change over time or in different settings?

[18] **D0001** – What is the expected beneficial effect of the technology on mortality?

[19] This section addresses the following assessment elements:
D0011 – What is the effect of the technology on patients' body functions?
D0005 – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006 – How does the technology affect progression (or recurrence) of the disease or health condition?

Fasting blood glucose

No evidence was found to answer this research question.

Nüchternblutzucker: keine Evidenz

Hypoglycaemia

No evidence was found to answer this research question.

Hypoglykämie: keine Evidenz

Insulin

Insulin independence

One NRSI reported on insulin independence in ICT patients and pancreas tissue transplants [10]. The study identified that 57% (19 of 33) of ICT participants reached insulin independence, compared to 76% (25 of 33) patients who underwent pancreas transplant at one month post-transplantation (p value not reported) [10]. It was noted by the study authors that islet cells can take weeks or months to begin producing insulin, while pancreatic tissue will typically produce insulin immediately upon transplantation, which indicates that the measure of insulin independence at one month post-transplant may not be appropriate to indicate the efficacy of ICT [10].

Insulinunabhängigkeit nach 1 Monat in 1 NRSI:

IZT: 57 %
PankreasTx: 76 %

Exogenous insulin requirement

No evidence was found to answer this research question.

exogenes Insulin: keine Evidenz

Islet cell graft failure

One NRSI investigated islet cell graft function and pancreas graft function [10]. A total of five of 60 patients experienced exhaustion of C-peptide secretion within four weeks post-transplant and 27% of participants reported measurements >0.3 ng/ml, indicating partial graft function [10].

C-Peptid-Werte >0,3 ng/ml: 27 % in 1 NRSI

Renal function

No evidence was found to answer this research question.

Nierenfunktion: keine Evidenz

Immunosuppression

No evidence was found to answer this research question.

Immunsuppression: keine Evidenz

Diabetes complications

No evidence was found to answer this research question.

sekundäre Diabeteskomplikationen: keine Evidenz

Quality of life[20]

No evidence was found to answer this research question.

Lebensqualität: keine Evidenz

[20] This section addresses the following assessment elements:
C0008 – How safe is the technology in comparison to the comparator(s)?
C0004 – How does the frequency or severity of harms change over time or in different settings?

Patient safety[21]

Complications and adverse events

Overall complication rate

No evidence was found to answer this research question.

Gesamtkomplikationsrate: keine Evidenz

Major and minor adverse events

In the single included NRSI comparing ICT to pancreas transplant patients [10] 13 AEs were attributed to ICT, compared to 41 associated with pancreas transplant [10]. A significantly greater number of patients in the pancreas transplant group experienced cytomegalovirus reactivation ($p<0.001$); however, there were no significant differences in the onset of other AEs including infections, bacterial sepsis and worsening kidney function [10]. Procedure-related AEs were also reported including blood transfusion (ICT, n=two vs pancreas transplant, n=14) and relaparotomy (0 vs 18) and thrombosis events (3 vs 13) including transplantectomy (12), fogarty (2) and transplectomy (7) associated only with the pancreatic transplant group [10].

AE: 13 bei IZT vs. 41 bei PankreasTx

mehr behandlungsbedingte Komplikationen bei PankreasTx

Length of hospital stay

Length of hospital stay was reported in one NRSI, comparing ICT patients with those undergoing pancreas tissue transplant [10]. A statistically significant difference in the average number of days spent in hospital was observed for the ICT group at 16 days (IQR 9-19), compared to the pancreas transplant group 19 days (IQR 16-24; p=0.009) [10].

Ø Tage im Krankenhaus: IZT: 16, PankreasTx: 19

Mortality[22]

T1D without kidney transplant

Survival rate

No evidence was found to answer this research question.

Überlebensrate: keine Evidenz

Procedure-related mortality

No evidence was found to answer this research question.

behandlungsbedingte Mortalität: keine Evidenz

[21] This section addresses the following assessment elements:
C0008 – How safe is the technology in comparison to the comparator(s)?
C0004 – How does the frequency or severity of harms change over time or in different settings?

[22] D0001 – What is the expected beneficial effect of the technology on mortality?

ICT single-arm evidence[23]

Glycaemic control

HbA1c

One case series was identified that reported on Hba1c in ICT patients with diabetes alone [12]. Median HbA1c levels were significantly reduced from 7.2% (55 mmol/mol) at baseline to 5.9% (41 mmol/mol) at day 75 and 5.6% (38 mmol/mol) at one year, respectively ($p<0.0003$) [12]. At one and two years of follow-up, HbA1c levels were <6.5% (48 mmol/mol) in 71% (38/48) ($p<0.001$) and 67% (33/48) ($p=0.02$) of patients, respectively [12].

HbA1c-Werte <6,5 % in 1 Fallserie:

1 Jahr FU: 71 %, 2 Jahre FU: 67 %

C-peptide secretion

Two single-arm studies reported on C-peptide levels within T1D patients following ICT [11, 12]. Percentages of ICT patients with C-peptide levels >0.3 ng/ml, which was used to indicate graft function, were at 95% and 94% at 75 days and one year, respectively, in one single-arm study [12]. The study also identified that C-peptide levels significantly increased in response to a mixed meal tolerance test, indicating the production of insulin by an islet graft [12]. In another single-arm study, C-peptide secretion >0.3 ng/ml was maintained at two years post-ICT in 70% of patients [11].

C-Peptid >0,3 ng/ml:

94 % nach 1 Jahr in 1 Fallserie, 70 % nach 2 Jahren in 1 Fallserie

Fasting blood glucose

No evidence was found to answer this research question.

Nüchternblutzucker: keine Evidenz

Hypoglycaemia

Two case series reported on the occurrence of hypoglycaemic events in ICT patients [11, 12]. A study by Herring et al. found that severe hypoglycaemic events eradicated with glycaemic control were achieved in 87.5% of patients (42 of 48) vs baseline ($p<0.001$) at one year, and 71% of patients (34 of 48) vs baseline ($p<0.01$) at two years in ICT patients [12]. It was also noted that all subjects enrolled within the study had experienced a severe hypoglycaemic event within the preceding twelve months, and only 4% (2 of 45) of patients experienced a severe hypoglycaemic episode within the following twelve months ($p<0.0003$) [12]. The same study also found that all patients in the study with residual islet function following ICT did not experience any severe hypoglycaemic episodes from 28 days to one year post-transplant [11].

ohne Hypoglykämien in 1 Fallserie: 71 % nach 2 Jahren

schwere Hypoglykämien in 1 Fallserie: 4 %

Insulin

Insulin independence

Insulin independence was reported in two case series [11, 12]. Hering at al. reported that 23% and 52.1% of participants were insulin independent at 75 days and one year, respectively, post-transplant [12]. Nearly half (2%, 20 of 48) of ICT recipients remained insulin dependent at two years post-transplant [12]. Insulin independence rates of 44%, 17% and 5% at one, two and three years, respectively were also reported in patients with varied numbers of islet transplants. [11].

Insulinunabhängigkeit unterschiedlich nach 1 Jahr FU in 2 Fallserien: 52 % vs. 17 %

[23] This section addresses the following assessment elements:
D0011 – What is the effect of the technology on patients' body functions?
D0005 – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006 – How does the technology affect progression (or recurrence) of the disease or health condition?

Exogenous insulin requirement

One single-arm study investigated median insulin use by ICT patients [12]. Hering et al. found that while patients required 0.49 units/kg of insulin at baseline, this reduced to 0.13 units/kg and 0.00 units/kg of insulin at day 17 and at one year post-transplant ($p<0.0003$) [12].

Insulinbedarf nach 1 Jahr stark reduziert in 1 Fallserie

Islet cell graft failure

Two case series studies reported islet graft function post-transplantation [11, 12]. In one study, 95% and 94% of participants reported C-peptide levels >0.3 ng/ml at 75 days and one-year post-transplant, indicating ongoing graft function [12]. In contrast another study identified that 28% of participants had complete graft loss at one-year post-transplant [11].

Transplantatverlust in 2 Fallserien: 6 % vs. 28 %

Renal function

Two case series studies reported on renal function post-ICT. One study utilised eGRF rates to identify ongoing kidney function, finding that compared to baseline, median eGFR decreased at 75 days (98 ml/min/1.73 m^2, IQR 42-140; $p=0.09$), and significantly decreased at one year (90 ml/min/1.73 m^2, IQR 59-129; $p=0.0008$) and two years (82 ml/min/1.73 m^2, IQR 54-123; $p<0.0001$) post-transplant [12]. Another study also identified a decrease in kidney function with ICT transplantation, with a decrease in creatine clearance (estimated decrease of 0.45 ml/min/1.73 m^2/month; $p=0.06$) and elevation in serum creatine (increase of 0.007 md/dL/month; $p=0.01$), which was associated with an increased incidence of albuminuria in some patients [11].

Nierenfunktion in 2 Fallserien:

signifikante Abnahme der eGFR im Verlauf

Kreatinin-Anstieg und vermehrte Albuminurie

Immunosuppression

No evidence was found to answer this research question.

Immunsuppression: keine Evidenz

Diabetes complications

One case series reported that no participants experienced the onset of any secondary diabetes complications post-ICT [11].

keine neuen diabetischen Sekundärkomplikationen in 1 Fallserie

Quality of life[24]

No evidence was found to answer this research question.

Lebensqualität: keine Evidenz

Patient safety[25]

Complications and adverse events

Overall complication rate

No evidence was found to answer this research question.

Gesamtkomplikationsrate: keine Evidenz

[24] This section addresses the following assessment elements:
C0008 – How safe is the technology in comparison to the comparator(s)?
C0004 – How does the frequency or severity of harms change over time or in different settings?

[25] This section addresses the following assessment elements:
C0008 – How safe is the technology in comparison to the comparator(s)?
C0004 – How does the frequency or severity of harms change over time or in different settings?

Major and minor adverse events

AEs were reported in two case series following ICT in T1D patients [11, 12]. As reported in one study 30 SAEs were reported in 21 patients from a total population of 48 within one year of follow-up, with 22 SAEs associated with the procedure, including onset of post-procedural bleeding associated with access to the hepatic portal vein required for the transplant, and eight attributed to causes not directly linked to the intervention [12]. An additional eight SAEs were reported at two years, including two infections associated with the use of immunosuppression and six not associated with the study protocol [12]. SAE vents that were attributed to the effects of an immunosuppression protocol, included neutropenia, pneumonia, gastrointestinal conditions and chest pain were reported by ICT patients in a separate study, with 25% of participants switching to an alternative immunosuppression regimen [11]. An additional 38 SAEs were reported, 61% of which were attributed to the study protocol, including intraperitoneal bleeding, venous occlusions and bile leaks [11]. One patient was also found to be experiencing severe hypoglycaemia attributed to immediate graft failure [11]. Minor AEs included mouth ulceration (92% of subjects), anaemia (81%), leukopenia (75%), diarrhoea (64%), headache (56%), neutropenia (53%), nausea (50%), vomiting (42%), acne (39%) and fatigue (39%) [11].

(S)AEs in 2 Fallserien:

1 Jahr FU:
30 SAEs bei 21/48 Pat., davon 22 verfahrensbedingt

häufigste leichte Nebenwirkungen:
Mundulzeration (92 %), Anämie (81 %), Leukopenie (75 %), Durchfall (64 %)

Length of hospital stay

No evidence was found to answer this research question.

Länge der Hospitalisierung: keine Evidenz

Mortality[26]

T1D without kidney transplant

Survival rate

One case series reported 100% survival rate post-ICT in T1D patients without a kidney transplant at two years follow-up [12].

100 % Überlebensrate in 1 Fallserie

Procedure-related mortality

No evidence was found to answer this research question.

behandlungsbedingte Mortalität: keine Evidenz

[26] **D0001** – What is the expected beneficial effect of the technology on mortality?

5 Certainty of evidence

ROB

The risk of bias (RoB) for individual outcomes of the included RCT was assessed using the Cochrane Risk of Bias 2 (RoB2) tool [64], with the RoB in NRSI assessed using the ROBINS-I tool [65].

ROB der Fallserien nicht erhoben

The RoB of single-arm studies was not assessed. According to the Health Technology Assessment Coordination Group (HTACG), uncontrolled trials are of very limited value for performing relative effectiveness assessment, therefore RoB assessment of single-arm trials is generally not required [75]. RoB of an uncontrolled study is very unlikely to be changed by a formal RoB assessment, thus single-arm studies were classified as having a high RoB.

Vertrauenswürdigkeit der Evidenz nach GRADE

The strength of evidence was rated individually according to GRADE schema [66] for the seven most crucial endpoints. A GRADE assessment was conducted for each population and separated by study design (e.g. RCT, NRSI). GRADE assessment was not carried out for the single-arm trials due to their high RoB. GRADE was conducted in GRADE pro by one reviewer and then validated by a second reviewer. Any disagreements were resolved via consensus or by a third reviewer. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [66].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate** = We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low** = Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The GRADE ranking for the research question can be found in table and in the evidence profile in Appendix Table A-12 to Table A-15.

Overall, the strength of evidence for the effectiveness and safety of ICT for all indications within this report was determined to be of very low certainty.

Table 5-1: Summary of findings for RCT: ICT compared to insulin therapy for T1D after kidney transplant

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with insulin therapy	Risk with ICT	Risk difference				
HBA1C <7% without severe hypoglycaemia follow-up: 6 months	Not estimable	Not estimable	Not estimable	RR 0.16 (0.06 to 0.39)	47 (1 RCT)	⨁◯◯◯ Very low[a,b]	Absolute effects not estimable due to 0 events in one treatment arm
C-peptide – not reported	-	-	-	-	-	-	-
Free from severe hypoglycaemia follow-up: 6 months	91 per 1,000	32 per 1,000 (18 to 58)	59 fewer per 1,000 (from 73 fewer to 33 fewer)	RR 0.352 (0.196 to 0.633)	47 (1 RCT)	⨁◯◯◯ Very low[a,b]	
β score ≥6 follow-up: 6 months	Not estimable	Not estimable	Not estimable	RR 0.360 (0.213 to 0.607)	47 (1 RCT)	⨁◯◯◯ Very low[a,b]	Absolute effects not estimable due to 0 events in one treatment arm
DQOL median gain in global score follow-up: 6 months	Median DQOL global score gain of -2 points	Median DQOL global score gain of 14 points	Median 16 points higher	-	46 (1 RCT)	⨁◯◯◯ Very low[a,b]	
Mortality Follow-up: 6 months	45 per 1,000	Not estimable	Not estimable	Not estimable	47 (1 RCT)	⨁◯◯◯ Very low[a,b]	Absolute and relative effects not estimable due to 0 events in one treatment arm
Procedural complications follow-up: 6 months	190 per 1,000	198 per 1,000 (60 to 660)	8 more per 1,000 (from 131 fewer to 470 more)	RR 1.040 (0.313 to 3.467)	47 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	

Abbreviations: CI … confidence interval, DQOL- diabetes quality of life, HRQOL … health-related quality of life, ICT … islet cell transplant, RCT … randomised controlled trial, RR … relative risk, T1D … type I diabetes

Notes:

RR and corresponding 95% CIs imputed by assessment group using the following formulas:

$RR = [a/(a + b)]/[c/(c + d)]$; *lower bound* $= exp[ln(RR) - Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$;

upper bound $= exp[ln(RR) + Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$.

Comments:

[a] *High risk of bias*

[b] *Sample size between 1-99 patients therefore downgraded 2 levels [76]*

[c] *CI crosses the null*

Table 5-2: Summary of findings for NRSI: ICT compared to insulin therapy for T1D

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with insulin therapy	Risk with ICT	Risk difference				
HbA1c **follow-up: 3 years**	Mean HBA1C of 8.1 percent	Mean HBA1C of 6.6 percent	MD 1.5 percent lower (NR)	-	30 (1 NRSI)	⨁◯◯◯ Very low[a,b]	
C-peptide **follow-up: 3 years**	**I:** 11/13 patients had blood C-peptide level <0.2 ng/mL **C:** NR				30 (1 NRSI)	⨁◯◯◯ Very low[a,b]	
Hypoglycemia **follow-up: 3 years**	Mean hypoglycemic events 1.7 events per week	Mean hypoglycemic events 0.7 events per week	MD 1 event per week lower (NR)	-	30 (1 NRSI)	⨁◯◯◯ Very low[a,b]	
Graft failure – not reported	-	-	-	-	-	-	-
HRQoL – not reported	-	-	-	-	-	-	-
Mortality **follow-up: 3 years**	Not estimable	Not estimable	Not estimable	Not estimable	30 (1 NRSI)	⨁◯◯◯ Very low[a,b]	No deaths reported in either treatment arm
Grade 3 or 4 adverse events **follow-up: 3 years**	**I:** 11/13 patients had blood C-peptide level <0.2 ng/mL **C:** NR				30 (1 NRSI)	⨁◯◯◯ Very low[a,b]	

Abbreviations: C … comparator, CI … confidence interval, HRQOL … health-related quality of life, I … intervention, ICT … islet cell transplant, MD … mean difference, NR … not reported, NRSI … non-randomised studies of interventions, T1D … type I diabetes

Notes:

RR and corresponding 95% CIs imputed by assessment group using the following formulas:

$RR = [a/(a + b)]/[c/(c + d)]$; *lower bound* $= exp[ln(RR) - Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$; *upper bound* $= exp[ln(RR) + Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$.

Comments:

[a] *ROBINS-I assessed to be of serious risk of bias*

[b] *Sample size between 1–99 patients therefore downgraded 2 levels [76]*

Table 5-3: Summary of findings for NRSI: ICT compared to pancreas transplant for T1D

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with pancreas transplant	Risk with ICT	Risk difference				
HbA1c– not reported	-	-	-	-	-	-	-
C-peptide – not reported	-	-	-	-	-	-	-
Hypoglycemia – not reported	-	-	-	-	-	-	-
Early graft failure **follow-up: 4 weeks**	212 per 1,000	151 per 1,000 (53 to 428)	62 fewer per 1,000 (from 159 fewer to 216 more)	RR 0.71 (0.25 to 2.02)	66 (1 NRSI)	⨁◯◯◯ Very low[a,b]	
HRQoL – not reported	-	-	-	-	-	-	-
Mortality **follow-up: 1 year**	30 per 1,000	Not estimable	Not estimable	Not estimable	66 (1 NRSI)	⨁◯◯◯ Very low[a,b]	Absolute and relative effects not estimable due to 0 events in one treatment arm
Adverse events **follow-up: 1 year**	**Pooled data: I vs C events:** CMV reactivation: 2 vs 21 (p<0.001) Other infections: 2 vs 5 ■ - Urinary tract infection: 0 vs 3 ■ -Bacterial sepsis: 0 vs 2 ■ Necrotizing fasciitis: 0 vs 1 Worsening kidney function: 5 vs 4 ■ -End-stage RD: 1 vs 2 ■ -Worsened DN: 1 vs 3 ■ -Resolved after TW: 2 vs 0 Other medical complications: ■ -Thrombotic TP: 0 vs 1 ■ -Toxic hepatitis: 1 vs 0 TAC-ind. Optic neuritis: 0 vs 1				66 (1 NRSI)	⨁◯◯◯ Very low[a,b]	Per patient data not reported

Abbreviations: C … comparator, CI … confidence interval, CMV … Cytomegalovirus, DN … diabetic nephropathy, HRQOL … health-related quality of life, I … intervention, ICT … islet cell transplant, NE … not estimable, NRSI … non-randomised studies of interventions, RD … renal disease, RR … relative risk, TAC … tacrolimus, T1D … type I diabetes, TP … thrombocytopenic purpura, TW –tacrolimus withdrawal

Notes:

RR and corresponding 95% CIs imputed by assessment group using the following formulas:

$RR = [a/(a + b)]/[c/(c + d)]$; *lower bound* $= exp[ln(RR) - Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$; *upper bound* $= exp[ln(RR) + Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$.

Comments:

[a] *ROBINS-I assessed to be of critical risk of bias*

[b] *Sample size between 1-99 patients therefore downgraded 2 levels [76]*

Table 5-4: Summary of findings for NRSI: ICT alone compared to ICT with kidney transplant for T1D

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with ICT plus kidney transplant	Risk with ICT alone	Risk difference				
HBA1C <7% without severe hypoglycaemia **Follow-up: median range 7.1 years to 8 years**	167 per 1,000	100 per 1,000 (72 to 140)	67 fewer per 1,000 (from 95 fewer to 27 fewer)	RR 0.60 (0.43 to 0.84)	72 (1 NRSI)	⨁◯◯◯ Very low[a,b]	
C-peptide **Follow-up: median range 7.1 years to 8 years**	**I:** Mean fasting C-peptide rose over the first 1 post-transplant year from undetectable levels to a peak of 1.7 ng/mL, decreased to 1.3 ng/mL at 3 years, then gradually to a mean of 1.2 ng/mL at the median follow-up of 5.6 years and 1.0 at 8 years. **C:** Mean fasting C-peptide rose over the first 1.2 post-transplant 4 years from undetectable levels to a peak of 2.0 ng/mL, and fell more rapidly to 1.5 ng/mL at the median follow-up of 3.3 years and 0.7 ng/mL at the end of follow-up at 7.1 years.				72 (1 NRSI)	⨁◯◯◯ Very low[a,b]	
Severe hypoglycaemic events **Follow-up: median range 7.1 years to 8 years**	83 per 1,000	63 per 1,000 (11 to 349)	21 fewer per 1,000 (from 73 fewer to 266 more)	RR 0.75 (0.13 to 4.19)	72 (1 NRSI)	⨁◯◯◯ Very low[a,b,c]	
Graft failure **Follow-up: range 39.3 months to 65.8 months**	375 per 1,000	154 per 1,000 (64 to 360)	221 fewer per 1,000 (from 311 fewer to 15 fewer)	RR 0.41 (0.17 to 0.96)	72 (1 NRSI)	⨁◯◯◯ Very low[a,b]	
HRQOL – not reported	-	-	-	-	-	-	-
Mortality **Follow-up: median range 7.1 years to 8 years**	Not estimable	Not estimable	Not estimable	Not estimable	72 (1 NRSI)	⨁◯◯◯ Very low[a,b]	No deaths reported in either treatment arm
Adverse events **Follow-up: median range 7.1 years to 8 years**	625 per 1,000	581 per 1,000 (394 to 862)	44 fewer per 1,000 (from 231 fewer to 237 more)	RR 0.93 (0.63 to 1.38)	72 (1 NRSI)	⨁◯◯◯ Very low[a,b]	

Abbreviations: C … comparator, CI … confidence interval, HRQOL … health-related quality of life, I … intervention, ICT … islet cell transplant, NRSI … non-randomised studies of interventions, RR … relative risk, T1D … type I diabetes

Notes:

RR and corresponding 95% CIs imputed by assessment group using the following formulas:

$RR = [a/(a + b)]/[c/(c + d)]$; *lower bound* $= \exp[\ln(RR) - Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$; *upper bound* $= \exp[\ln(RR) + Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$.

Comments:

[a] *ROBINS-I assessed to be of moderate risk of bias*

[b] *Sample size between 1–99 patients therefore downgraded 2 levels [76]*

[c] *CI crosses the null and relatively wide*

6 Discussion

The objective of this review was to assess the clinical effectiveness and safety of ICT (with or without kidney transplant) for treating patients with CP and T1D compared to standard care consisting of pharmacotherapy, non-pharmacotherapy or a combination of both. Across the three populations, a total of eleven studies met the pre-defined inclusion criteria.

Bewertung klinischer Wirksamkeit und Sicherheit von Inselzelltransplantation

6.1 Summary of evidence

6.1.1 Chronic pancreatitis

Case series evidence

The evidence-base for CP was limited to three prospective single-arm case series. Overall, the strength of evidence for the safety and effectiveness of ICT for CP is very low [1-3].

CP: 3 Fallserien mit sehr niedriger Evidenz

Although slight increases in HbA1c were identified following the intervention, there were no significant differences from baseline measures up to three years post-transplant [1-3]. C-peptide levels remained stable from pre- to post-transplant in one study, and one study revealed stable fasting blood glucose levels from baseline to three years post-ICT [1-3]. Insulin independence ranged at short-term timepoints, with 17.6% of participants recording insulin independence in one study with a ten-year timepoint [1-3]. Many patients who undergo pancreatectomy and ICT do not experience significant endocrine issues attributed to CP. Therefore, following pancreas removal and autologous ICT transplant, glycaemic control is expected to remain steady following the intervention [1-3].

stabile Blutzuckerwerte über mehrere Jahre

Insulinunabhängigkeit bei 17,6 % der Patient:innen nach 10 Jahren

Significant differences in pain among participants following ICT and pancreatectomy were reported for up to three years, indicating reduced pain compared to baseline. These findings are substantiated by reductions in analgesia use [1-3]. Two case studies reported approximately 70% of patients not requiring the ongoing use of analgesia, with another study reporting significant reductions in morphine use for up to three years post-ICT and pancreatectomy, compared with baseline [1-3].

Analgetikagabe in 2 Fallserien bei ca. 70 % der Patient:innen nicht mehr nötig

Quality of life

One case series reported improvements in a range of HQoL measures at two years. Compared with baseline, there were statistically and clinically significant improvements in domains of global and functional health. There were also statistically significant improvements in all domains of the pancreas specific EORTC QLQ-PAN26 [3].

Lebensqualität: statistisch und klinisch signifikante Verbesserungen in 1 Fallserie

Safety

No studies reported complications or adverse events.

Sicherheit: keine Evidenz

6.1.2 T1D and kidney transplant

One RCT, two NRSIs and three single-arm case series were available for the population of T1D patients with severe hypoglycaemia and kidney transplant [4-9]. Overall, the strength of evidence for ICT in patients with T1D and kidney transplant compared with insulin therapy or compared to ICT with kidney transplant is very low.

T1D mit NierenTx:
1 RCT, 2 NRSI und
3 einarmige Fallserien

RCT evidence: ICT with kidney transplant vs insulin therapy

Evidence from one RCT showed significantly higher β-scores, significantly reduced HbA1c and a significantly larger proportion of patients recording HbA1c levels <7%, suggesting more optimal glycaemic control in ICT patients compared to those undergoing conventional insulin therapy for T1D management at six months [4]. No significant reductions in fasting blood glucose were identified between ICT patients and insulin patients; however, a significant reduction in hypoglycaemia events were recorded in ICT patients [4]. Over 50% of patients in the ICT population achieved insulin independence and approximately 93% of patients had a functioning islet graft at twelve months post-transplant [4]. Kidney function was also significantly improved in ICT patients and insulin therapy patients. Such findings suggest that ICT may be associated with improved glycaemic control compared to insulin therapy alone in this population. Kidney function, as assessed by eGFR, was significantly improved in both ICT and insulin therapy patients at twelve months compared to baseline [4].

RCT:
IZT + NierenTx vs.
Insulintherapie (IT)

weniger Hypoglykämien
in IZT-Gruppe

50 % insulinunabhängig,
Transplantatfunktion bei
93 % nach 1 Jahr

NRSI evidence: ICT with kidney transplant vs insulin therapy

Significant decreases in HbA1c for longer periods and reduced overall HbA1c for up to three years was noted for ICT patients, compared with patients who underwent insulin therapy [8]. Significant differences in the number of hypoglycaemic events were also identified in ICT patients, compared to insulin therapy at all follow-up times, with many ICT patients reaching insulin independence and requiring significantly less exogenous insulin during follow-up [8]. There were also improvements in fasting blood glucose for ICT compared with insulin therapy at up to three years [8].

1 NRSI:
IZT + NierenTx vs.
Insulintherapie

weniger Hypoglykämien
& besserer
Nüchternblutzucker
bis 3 Jahre FU

NRSI evidence: ICT with kidney transplant vs ICT without kidney transplant

Measurements of HbA1c, C-peptide, hypoglycaemia and insulin independence indicate similar or slightly improved glycaemic control in patients who receive a kidney transplant plus ICT, compared to patients who receive ICT alone [5]. In addition to a greater proportion of ICT and kidney transplant patients maintaining an optimal HbA1c level of <6.5%, C-peptide remained slightly higher within this group [5]. Similar numbers of patients with ICT plus kidney transplant and ICT alone experienced insulin independence and had islet graft function at 8.3 years follow-up [5]. In addition, kidney function was observed to be slightly improved in ICT plus kidney transplant patients, likely owing to transplant of healthier tissue following the onset of kidney disease [5].

1 NRSI:
IZT + NierenTx vs.
IZT allein

Insulinunabhängigkeit und
Transplantatfunktion nach
8 Jahren ähnlich in beiden
Gruppen

Case series evidence

3 Fallserien:

Insulinunabhängigkeit bei ca. 1/3 der Patient:innen nach 2 Jahren

All three single-arm studies showed statistically significant reductions in HbA1c up to ten years post-transplant, in addition to one study that found gradually increasing C-peptide levels up to three years post-ICT [6, 7, 9]. A reduced amount of time spent in hypoglycaemia at most timepoints was also identified. In one case series, insulin independence was maintained in approximately one third of patients at two years post-transplant [6, 7, 9]. A significant reduction in insulin required post-transplant was also identified at up to ten years post-transplant. Improvements in fasting blood glucose varied across the studies, as well as kidney function [6, 7, 9].

Quality of life

Lebensqualität verbessert

For quality of life, there were improvements in SF-36 general health perceptions and health transition compared with insulin therapy alone, and improvements in baseline for diabetes distress scores, the Hypoglycaemia Fear Score and the EuroQOL overall health state [7].

Safety

mehrere SAEs in 1 RCT und 1 NRSI

For safety outcomes, the RCT showed procedure-related complications in 19.1% and AEs in 42.6% of ICT plus kidney transplant patients [4]. One NRSI reported SAEs in 56–62.5% of patients in the ICT alone and ICT with kidney transplant, respectively [5]. For insulin-only patients, there was one recorded SAE in the RCT, and ten grade three and one grade four SAE reported in the NRSI [8].

6.1.3 T1D patients, ICT only (no kidney transplant)

T1D ohne NierenTx: 1 NRSI, 2 Fallserien

One NRSI (comparing ICT to pancreas transplant) and two case series were identified for T1D patients [10-12]. Overall, the strength of evidence for ICT in patients with T1D compared with pancreas transplant or insulin therapy is very low. It is noted that the comparison of ICT and pancreas transplant has limited clinical relevance as patient selection for these interventions differs in usual practice (expert clinical advice). In addition, the patient selection criteria for each population differed in the NRSI, and there are differences in the invasiveness and safety profile of each intervention. This comparison has been left in the report for information and is in line with the pre-determined PICO, but should be interpreted with caution.

NRSI evidence

kaum Daten zu Blutzuckerkontrolle in 1 NRSI

Glycaemic control was poorly reported in the NRSI, with no HbA1c, fasting blood glucose or hypoglycaemia outcomes provided. At one month post-transplant a greater proportion of patients were insulin-independent in the pancreas transplant group compared to ICT patients, with the authors suggesting this was a result of a delay in the ICT to produce insulin [10].

Case series evidence

Insulinunabhängigkeit variierte zwischen Fallserien

In one case series, HbA1c levels were significantly reduced at one year, with 67% of patients maintaining HbA1c levels at <6.5% at two years. C-peptide levels – indicating a successful graft – were reported in two case series as >0.3 ng/ml in 70–94% of patients at one to two years [11, 12]. Two case series reported a significant reduction in hypoglycaemic events at one to two years. Insulin independence varied across the two case series. Renal function reduced from baseline, with a decrease in eGFR at two years as well as decreases in creatinine clearance [11, 12].

Quality of life

Lebensqualität: keine Evidenz

No included study reported on HRQoL outcomes in this population.

Safety

mehr verfahrensbedingte AE bei PankreasTx vs. IZT in 1 NRSI

No included study described overall complication rates. In the NRSI, there were more procedure-related AEs in the pancreas transplant group compared with the ICT group. Pancreas transplant patients reported more cytomegalovirus reactivation, but there were no differences in other AEs (e.g. infection, kidney function) [10]. AEs were also reported in the case series, including procedure- and immunosuppression-related AEs associated with ICT [10].

6.2 Evidence gaps

überwiegend einarmige Fallserien mit begrenzter prospektiver Vergleichsevidenz

The lack of prospective RCTs comparing ICT with alternative therapies across all populations is one of the largest limitations identified within the current report This may be as ICT is often a last resort for patients who have failed best medical therapy. A large proportion of the available evidence is single-arm case series, with a limited amount of prospective comparative evidence. While these studies can provide long-term follow-up, they are unable to assess the efficacy of the therapy in comparison to other treatment options available for both CP and T1D patients. Further, the comparative studies only assessed the efficacy of insulin therapy and pancreas tissue transplant for T1D, with no comparative evidence identified comparing the therapy to alternative treatments for CP patients following pancreatectomy.

heterogene Berichterstattung erschwert Vergleichbarkeit

As previously identified, some outcomes were not covered by studies included for each population, with some populations lacking long-term safety and efficacy data, even though this may be covered in studies for other populations. Additionally, the reporting methods for each of the outcomes was heterogenous, with outcomes difficult to compare within populations. Although current evidence indicates similar efficacy of treatment across all groups, it is unclear if outcomes for T1D and CP can supplement each other, and if the efficacy and safety of ICT will differ for patients with different indications for the therapy, particularly for patients with T1D with or without a kidney transplant. The limited, or lack of evidence comparing the therapy to alternatives associated with ongoing management of diabetes or CP in both adult and paediatric populations suggests the need for continued research into the therapy and its effectiveness across different patient populations, particularly

Bedarf an hochwertigen RCTs und Vergleichsstudien

high quality RCTs and NRSIs investigating the range of alternatives including pancreas transplantation, ongoing best practice and alternative medical therapies.

Evidenzlücken

Within the CP population, no evidence was available for hypoglycaemic events, islet cell graft failure, AEs and complications. Within the T1D plus kidney transplant population, no prospective evidence was available for length of hospital stay or procedure-related mortality, while for the T1D alone group, fasting blood glucose, overall complication rate and procedure-related mortality were not reported. The lack of evidence for specific indications of ICT within certain populations confirms the need for further studies into ICT and its safety and efficacy outcomes.

systematische Reviews und HTAs zu Inselzelltransplantation bei CP

basieren auf limitierter Evidenz

Although a formal review of previous policy decisions was not undertaken for this report, recent published systematic reviews and HTAs conclude that autologous ICT is an option for CP patients following total pancreatectomy [56, 77-79]. A recent guideline includes this intervention as an option for highly selected patients with refractory chronic pain in which all other symptom control measures have failed, but indicates that the available evidence is limited [17]. Outcomes are commonly limited to before-and-after results of insulin independence and pain, and the majority of studies (16 of 21) are of retrospective design (no RCTs) and with significant heterogeneity across studies [77, 78].

systematische Reviews zu T1D + IZT

Verbesserungen bei Gesundheitsergebnissen

Similarly, for T1D, previous systematic reviews and HTAs have concluded that ICT is associated with improvements in health outcomes [56, 59, 80, 81]. The evidence-base for this population includes one RCT, a small number (3-6) of prospective and retrospective NRSIs, and case series evidence. Outcome reporting varies, with most studies reporting glycaemic control and AEs [59]. There were significant improvements in quality of life in T1D patients after ICT, with or without kidney transplant, although reporting is heterogeneous [80]. Further information on the recent HTA can be found in the Appendix. Improvements in study reporting (including RCTs), with larger sample sizes and appropriate follow-up, are needed for an accurate appraisal of ICT [81].

retrospektive Studien bestätigen Ergebnisse der prospektiven Studien

As shown from the above systematic reviews, while this AIHTA analysis focused on prospectively designed studies, the broader evidence-base for ICT includes many retrospective studies. These studies provide further information and in general support the prospective information provide in this report.

französische Registerdaten: Verbesserungen bei IZT + NierenTx

A review of French registry data provided evidence for patient-graft survival in ICT after kidney transplant compared with kidney transplant alone in patients T1D [47]. In comparing 40 patients who received ICT and kidney compared to 80 patients who received kidney transplant alone, with a follow-up of up to 16 years, glycaemic control in ICT patients was maintained, with a probability of insulin requirement of 61.2% at ten years. In addition, there was a significant benefit for ICT and overall patient-graft survival (HR 0·44, 95% CI 0·23–0·88; p=0·022) and a protective effect of ICT and the probability of death (HR 0·41, 95% CI 0·13–0·91; p=0·042). These improvements are in line with the evidence formally included in this report.

Langzeitdaten aus Italien und Kanada für T1D: Insulinunabhängigkeit bei 32-44 % nach 5-6 Jahren

Further long-term data is provided for ICT transplant (alone) for T1D in two single centre studies from Italy and Canada. These results allow a comparison of factors which led to improved patient outcomes. Patients maintained insulin independence for 32% (25–39) at five years or 44% to a median of six years [82, 83]. Data from the Collaborative Islet Transplant Registry and the

T1D Exchange Registry also showed an improvement in glycaemic control for ICT patients compared with ongoing standard of care over five years, although with a greater decline in kidney function [84]. This data supports prospective evidence and shows that glycaemic control in T1D can be maintained following ICT.

Similarly for ICT in patients with CP, recent retrospective studies show a maintenance of stable glycaemic control of up to ten or twelve years from baseline, in line with long-term results of prospective data [85].

CP: stabile Blutzuckerkontrolle bis 10-12 Jahre nach IZT

6.3 Ongoing clinical trials

To address gaps in the currently available prospective evidence base for ICT, several clinical trial registries were searched for ongoing clinical studies of the intervention. In patients with CP, one RCT and one randomised pilot trial of patients were identified, investigating the outcomes of ICT and ICT combined with the concomitant transplantation of mesenchymal stem cells and omental pouch islet cells, respectively. Outcomes to be investigated include changes in glycaemic control, changes in islet cell function, AEs, insulin use and Clarke score. These studies are being conducted at universities in the US, with one study reported as complete in 2024 and the other with a suggested completion date of June 2026. For T1D, a randomised, prospective, medico-economic nationwide French study for investigation of ICT compared to insulin therapy for patients with brittle T1D, and a phase II trial to investigate ICT via the hepatic portal vein compared to ICT into the omentum are in progress. Outcomes anticipated to be reported within these studies include cost-utility ratio and glycaemic control. These studies are set to be completed in France and Italy, with one study of unknown status as of 2023 and the other currently reported as active.

laufende relevante Studien:

CP: 1 RCT und 1 randomisierte Pilotstudie

T1D: 1 RCT und 1 Phase-II-Studie

6.4 Limitations

The methodology of this review has numerous advantages, including a systematic and thorough search for evidence, with study selection and data extraction duplicated by two reviewers. However, systematic reviews have shortcomings. For this review, evidence was restricted to prospective studies, which are structured to limit problems associated with retrospective research, such as inconsistencies in patient selection and outcomes reporting. Unfortunately, the included studies remained limited in the risk of bias and overall quality assessment conducted via GRADE. However, it is unlikely that retrospective studies would materially change the overall evidence base.

Beschränkung auf prospektive Studien

Due to the varied and limited evidence base across each population, quantitative synthesis of the outcomes was also not frequently possible, with high heterogeneity between outcomes within populations. Within each population, some efficacy outcomes did not have evidence reported by the included studies. Additionally, few studies reported confidence intervals and minimal clinically important difference values within outcomes, making the results dif-

Einschränkungen der Evidenzsynthese

ficult to interpret regarding clinical significance. Comparative evidence was limited, with only one RCT available across all populations. For T1D (no kidney transplant), comparative evidence is limited to ICT versus pancreas transplant. However, a more appropriate comparator in this population may be continued insulin therapy as published guidelines (and as supported by clinical expert advice) commonly have different selection criteria for pancreas transplant and ICT. In the future, local clinical guidelines will be valuable to provide advice in terms of use of these therapies and patient selection.

Studienstandorte

Locations of the included trials were countries in Europe (France and Italy), as well as the US and Canada. These populations are likely to be representative of the Austrian population.

6.5 Conclusions

6.5.1 CP

unzureichende Evidenz für Zusatznutzen von IZT bei CP

In summary, for patients with CP following total pancreatectomy there was a very low certainty of evidence. Data from three case series suggests that ICT can help with the symptoms of pain and HRQoL, with results reported to ten years. There are ongoing insulin requirements in most patients. The benefits of ICT compared with other interventions is uncertain.

6.5.2 T1D with kidney transplant

Hinweis für einen Zusatznutzen mit sehr geringer Evidenz für IZT bei T1D mit Nierentransplantation

In summary, the evidence for patients with T1D plus kidney transplant suggest that ICT, compared with insulin therapy, can improve glycaemic control. Graft survival decreases over time, with results available up to eight years follow-up. Some quality-of-life measures improved, and the intervention is associated with some procedural complications and AEs. The evidence was based on a very low certainty of evidence. However, evidence from a single RCT with small patient numbers showed significant improvements in glycaemic scores (HbA1c and severe hypoglycaemia).

6.5.3 T1D without kidney transplant

unzureichende Evidenz für Zusatznutzen von IZT bei T1D ohne Nierentransplantation

For T1D without kidney transplant, the evidence was very low certainty, from one NRSI and two case series, with no long-term follow-up. There were improvements from baseline for measures of glycaemic control, but other reported outcomes varied across studies (e.g. insulin independence and graft survival). Short-term evidence (one month) showed inferior outcomes for ICT compared with pancreas transplant for insulin independence. There were fewer AEs for ICT compared to pancreas transplant. Quality of life outcomes were not reported.

7 Evidence based conclusion

7.1 Chronic pancreatitis

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-1: Evidence based conclusions population one

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
	2b	Less robust evidence indicating an added benefit in routine use or in specific indications
X	3	**No evidence or inconclusive evidence available to demonstrate an added benefit of the intervention of interest.**
	4	Strong evidence indicates that intervention is ineffective and or harmful.

Reasoning:

The current evidence is not sufficient to prove, that the assessed technology ICT is effective and safe. New study results will potentially influence the effect estimate considerably.

Evidenz unzureichend: IZT bei CP derzeit nicht empfohlen

The re-evaluation is recommended beyond 2027.

Re-Evaluierung frühestens 2027

7.2 Type 1 diabetes with kidney transplant

InTable 7-2 the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-2: Evidence based conclusions population two

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
X	2b	**Less robust evidence indicating an added benefit in routine use or in specific indications**
	3	No evidence or inconclusive evidence available to demonstrate an added benefit of the intervention of interest.
	4	Strong evidence indicates that intervention is ineffective and or harmful.

Reasoning:

The current evidence indicates that the assessed technology ICT only under certain conditions is as effective and safe than the comparators insulin therapy. New study results will potentially influence the effect estimate considerably.

IZT: Hinweis für Zusatznutzen

The re-evaluation is recommended beyond 2027.

Re-Evaluierung frühestens 2027

7.3 Type 1 diabetes without kidney transplant

In the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-3: Evidence based conclusions population three

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
	2b	Less robust evidence indicating an added benefit in routine use or in specific indications
X	3	**No evidence or inconclusive evidence available to demonstrate an added benefit of the intervention of interest.**
	4	Strong evidence indicates that intervention is ineffective and or harmful.

Reasoning:

The current evidence is not sufficient to prove, that the assessed technology ICT is as effective and safe as pancreas transplant. New study results will potentially influence the effect estimate considerably.

Evidenz unzureichend, ICT bei T1D ohne Nierentransplantation derzeit nicht empfohlen; Re-Evaluierung frühestens 2027

The re-evaluation is recommended beyond 2027.

8 References

[1] Pollard CA, Chung WY, Garcea G, Dennison AR. Assessment of long-term graft function following total pancreatectomy and autologous islet transplantation: the Leicester experience. Hepatobiliary Surg Nutr. 2023;12(5):682-91.

[2] Gruessner RWG, Cercone R, Galvani C, Rana A, Porubsky M, Gruessner AC, et al. Results of Open and Robot-Assisted Pancreatectomies With Autologous Islet Transplantations: Treating Chronic Pancreatitis and Preventing Surgically Induced Diabetes. Transplantation Proceedings. 2014;46(6):1978-9.

[3] Coluzzi M, Takita M, Saracino G, Rub Hakim Mohammed A, Darden CM, Testa G, et al. Improved Quality of Life Among Chronic Pancreatitis Patients Undergoing Total Pancreatectomy With Islet Autotransplantation-Single Center Experience With Large Cohort of Patients. Transpl Int. 2023;36:11409.

[4] Lablanche S, Vantyghem MC, Kessler L, Wojtusciszyn A, Borot S, Thivolet C, et al. 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. Lancet Diabetes Endocrinol. 2018;6(7):527-37.

[5] Rickels MR, Eggerman TL, Bayman L, Qidwai JC, Alejandro R, Bridges ND, et al. Long-term Outcomes With Islet-Alone and Islet-After-Kidney Transplantation for Type 1 Diabetes in the Clinical Islet Transplantation Consortium: The CIT-08 Study. Diabetes Care. 2022;45(12):2967-75.

[6] Vantyghem MC, Chetboun M, Gmyr V, Jannin A, Espiard S, Le Mapihan K, et al. Ten-Year Outcome of Islet Alone or Islet After Kidney Transplantation in Type 1 Diabetes: A Prospective Parallel-Arm Cohort Study. Diabetes Care. 2019;42(11):2042-9.

[7] Markmann JF, Rickels MR, Eggerman TL, Bridges ND, Lafontant DE, Qidwai J, et al. Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes. Am J Transplant. 2021;21(4):1477-92.

[8] Vantyghem MC, Marcelli-Tourvieille S, Fermon C, Duhamel A, Raverdy V, Arnalsteen L, et al. Intraperitoneal insulin infusion versus islet transplantation: comparative study in patients with type 1 diabetes. Transplantation. 2009;87(1):66-71.

[9] Vantyghem MC, Raverdy V, Balavoine AS, Defrance F, Caiazzo R, Arnalsteen L, et al. Continuous glucose monitoring after islet transplantation in type 1 diabetes: an excellent graft function (β-score greater than 7) Is required to abrogate hyperglycemia, whereas a minimal function is necessary to suppress severe hypoglycemia (β-score greater than 3). J Clin Endocrinol Metab. 2012;97(11):E2078-83.

[10] Maffi P, Scavini M, Socci C, Piemonti L, Caldara R, Gremizzi C, et al. Risks and benefits of transplantation in the cure of type 1 diabetes: whole pancreas versus islet transplantation. A single center study. Rev Diabet Stud. 2011;8(1):44-50.

[11] Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med. 2006;355(13):1318-30.

[12] Hering BJ, Clarke WR, Bridges ND, Eggerman TL, Alejandro R, Bellin MD, et al. Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia. Diabetes Care. 2016;39(7):1230-40.

[13] Atkinson MA, Campbell-Thompson M, Kusmartseva I, Kaestner KH. Organisation of the human pancreas in health and in diabetes. Diabetologia. 2020;63(10):1966-73.

[14] Rahman MS, Hossain KS, Das S, Kundu S, Adegoke EO, Rahman MA, et al. Role of Insulin in Health and Disease: An Update. Int J Mol Sci. 2021;22(12).

[15] Yang D, Forsmark CE. Chronic pancreatitis. Curr Opin Gastroenterol. 2017;33(5):396-403.

[16] Dominguez-Munoz JE, Drewes AM, Lindkvist B, Ewald N, Czakó L, Rosendahl J, et al. Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis. Pancreatology. 2018;18(8):847-54.

[17] Gardner TB, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. ACG Clinical Guideline: Chronic Pancreatitis. Official journal of the American College of Gastroenterology | ACG. 2020;115(3).

[18] Hart PA, Conwell DL. Chronic Pancreatitis: Managing a Difficult Disease. Am J Gastroenterol. 2020;115(1):49-55.

[19] Ouyang G, Pan G, Liu Q, Wu Y, Liu Z, Lu W, et al. The global, regional, and national burden of pancreatitis in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. BMC Medicine. 2020;18(1):388.

[20] Skube ME, Beilman GJ. Surgical treatment of pain in chronic pancreatitis. Curr Opin Gastroenterol. 2018;34(5):317-21.

[21] Wilson GC, Turner KM, Delman AM, Wahab S, Ofosu A, Smith MT, et al. Long-Term Survival Outcomes after Operative Management of Chronic Pancreatitis: Two Decades of Experience. J Am Coll Surg. 2023;236(4):601-10.

[22] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021 Seattle, United States: Institute for Health Metrics and Evaluation (IHME); 2021 [

[23] Lévy P, Domínguez-Muñoz E, Imrie C, Löhr M, Maisonneuve P. Epidemiology of chronic pancreatitis: burden of the disease and consequences. United European Gastroenterol J. 2014;2(5):345-54.

[24] Hall TC, Garcea G, Webb MA, Al-Leswas D, Metcalfe MS, Dennison AR. The socio-economic impact of chronic pancreatitis: a systematic review. J Eval Clin Pract. 2014;20(3):203-7.

[25] Stauffer JA, Nguyen JH, Heckman MG, Grewal MS, Dougherty M, Gill KR, et al. Patient outcomes after total pancreatectomy: a single centre contemporary experience. HPB (Oxford). 2009;11(6):483-92.

[26] DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018;391(10138):2449-62.

[27] Ilonen J, Lempainen J, Veijola R. The heterogeneous pathogenesis of type 1 diabetes mellitus. Nature Reviews Endocrinology. 2019;15(11):635-50.

[28] Akil AA, Yassin E, Al-Maraghi A, Aliyev E, Al-Malki K, Fakhro KA. Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era. J Transl Med. 2021;19(1):137.

[29] Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am. 2010;39(3):481-97.

[30] Cryer PE. Hypoglycemia in type 1 diabetes mellitus. Endocrinol Metab Clin North Am. 2010;39(3):641-54.

[31] Rami-Merhar B, Hofer SE, Fröhlich-Reiterer E, Waldhoer T, Fritsch M. Time trends in incidence of diabetes mellitus in Austrian children and adolescents <15 years (1989-2017). Pediatr Diabetes. 2020;21(5):720-6.

[32] Brown CT, Davis-Richardson AG, Giongo A, Gano KA, Crabb DB, Mukherjee N, et al. Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. PLoS One. 2011;6(10):e25792.

[33] Erkkola M, Nwaru BI, Viljakainen HT. Chapter Ten – Maternal Vitamin D During Pregnancy and Its Relation to Immune-Mediated Diseases in the Offspring. In: Litwack G, editor. Vitamins & Hormones. 86: Academic Press; 2011. p. 239-60.

[34] Haslwanter V, Rochau U, Siebert U, Schönherr HR, Oberaigner W. A population-based cohort of adult patients with diabetes mellitus in a Western District of Austria: The Diabetes Landeck cohort. Endocrinol Diabetes Metab. 2023;6(2):e395.

[35] Amiel SA. The consequences of hypoglycaemia. Diabetologia. 2021;64(5):963-70.

[36] Jalal M, Campbell JA, Hopper AD. Practical guide to the management of chronic pancreatitis. Frontline Gastroenterology. 2019;10(3):253.

[37] Seicean A, Vultur S. Endoscopic therapy in chronic pancreatitis: current perspectives. Clin Exp Gastroenterol. 2015;8:1-11.

[38] Holt RIG, DeVries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2021;64(12):2609-52.

[39] National Institute for Health Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management. 2024.

[40] McCall M, Shapiro AM. Islet cell transplantation. Semin Pediatr Surg. 2014;23(2):83-90.

[41] Shapiro AMJ, Pokrywczynska M, Ricordi C. Clinical pancreatic islet transplantation. Nature Reviews Endocrinology. 2017;13(5):268-77.

[42] Matsumoto S. Clinical allogeneic and autologous islet cell transplantation: update. Diabetes Metab J. 2011;35(3):199-206.

[43] Gamble A, Pepper AR, Bruni A, Shapiro AMJ. The journey of islet cell transplantation and future development. Islets. 2018;10(2):80-94.

[44] Quintana JM, Stinchcomb AL, Kostyo JH, Robichaud BM, Plunk MA, Kane RR. Chemical Strategies for Improving Islet Transplant Outcomes. OBM Transplantation. 2018;02(04):036.

[45] Wang Q, Huang YX, Liu L, Zhao XH, Sun Y, Mao X, et al. Pancreatic islet transplantation: current advances and challenges. Front Immunol. 2024;15:1391504.

[46] Rickels MR, Robertson RP. Pancreatic Islet Transplantation in Humans: Recent Progress and Future Directions. Endocr Rev. 2019;40(2):631-68.

[47] Maanaoui M, Lenain R, Foucher Y, Buron F, Blancho G, Antoine C, et al. Islet-after-kidney transplantation versus kidney alone in kidney transplant recipients with type 1 diabetes (KAIAK): a population-based target trial emulation in France. Lancet Diabetes Endocrinol. 2024;12(10):716-24.

[48] Gaba RC, Garcia-Roca R, Oberholzer J. Pancreatic islet cell transplantation: an update for interventional radiologists. J Vasc Interv Radiol. 2012;23(5):583-94; quiz 94.

[50] Kochar IS, Jain R. Pancreas transplant in type 1 diabetes mellitus: the emerging role of islet cell transplant. Ann Pediatr Endocrinol Metab. 2021;26(2):86-91.

[51] Bellin MD, Dunn TB. Transplant strategies for type 1 diabetes: whole pancreas, islet and porcine beta cell therapies. Diabetologia. 2020;63(10):2049-56.

[52] Cerise A, Nagaraju S, Powelson JA, Lutz A, Fridell JA. Pancreas transplantation following total pancreatectomy for chronic pancreatitis. Clin Transplant. 2019;33(12):e13731.

[56] Haute Autorité de Santé. Transplantation d'îlots pancréatiques. Saint-Denis La Plaine; 2020.

[57] National health and Medical Research Council. Autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy. 2008.

[58] Al-Naseem AO, Attia A, Gonnah AR, Al-Naseem A, Spiers HVM, Gruessner A, et al. Pancreas transplantation today: quo vadis? Eur J Endocrinol. 2023;188(4):R73-r87.

[59] Institute of Health E. IHE Systematic Reviews. Islet Transplantation for the Treatment of Type 1 Diabetes. Edmonton, Alberta, Canada: Institute of Health Economics (IHE)

[60] Collaborative Islet Transplant Registry. Collaborative Islet Transplant Registry n.d.

[61] Yue L, Li J, Yao M, Song S, Zhang X, Wang Y. Cutting edge of immune response and immunosuppressants in allogeneic and xenogeneic islet transplantation. Front Immunol. 2024;15:1455691.

[62] Vidigal AC, de Lucena DD, Beyerstedt S, Rangel É B. A comprehensive update of the metabolic and toxicological considerations for immunosuppressive drugs used during pancreas transplantation. Expert Opin Drug Metab Toxicol. 2023;19(7):405-27.

[63] Amorese G, Lombardo C, Tudisco A, Iacopi S, Menonna F, Marchetti P, et al. Induction and Immunosuppressive Management of Pancreas Transplant Recipients. Curr Pharm Des. 2020;26(28):3425-39.

[64] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.

[65] Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

[66] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.

[67] Ryan EA, Paty BW, Senior PA, Lakey JRT, Bigam D, Shapiro AMJ. β-Score : An assessment of β-cell function after islet transplantation. Diabetes Care. 2005;28(2):343-7.

[68] Rickels MR, Robertson RP. Pancreatic Islet Transplantation in Humans: Recent Progress and Future Directions. Endocrine Reviews. 2018;40(2):631-68.

[69] Tharavanij T, Betancourt A, Messinger S, Cure P, Leitao CB, Baidal DA, et al. Improved long-term health-related quality of life after islet transplantation. Transplantation. 2008;86(9):1161-7.

[70] Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, et al. Five-Year Follow-Up After Clinical Islet Transplantation. Diabetes. 2005;54(7):2060-9.

[71] Baidal DA, Ballou CM, Rickels MR, Berney T, Pattou F, Payne EH, et al. Predictive Value of C-Peptide Measures for Clinical Outcomes of β-Cell Replacement Therapy in Type 1 Diabetes: Report From the Collaborative Islet Transplant Registry (CITR). Diabetes Care. 2023;46(4):697-703.

[72] Bellin MD, Forlenza GP, Majumder K, Berger M, Freeman ML, Beilman GJ, et al. Total Pancreatectomy With Islet Autotransplantation Resolves Pain in Young Children With Severe Chronic Pancreatitis. J Pediatr Gastroenterol Nutr. 2017;64(3):440-5.

[73] Georgiev G, Beltran del Rio M, Gruessner A, Tiwari M, Cercone R, Delbridge M, et al. Patient quality of life and pain improve after autologous islet transplantation (AIT) for treatment of chronic pancreatitis: 53 patient series at the University of Arizona. Pancreatology. 2015;15(1):40-5.

[74] National Health and Medical Research Council. Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods. Canberra: National Health and Medical Research Council; 2016.

[75] Directorate-General for Health and Food Safety. Guidance on the validity of clinical studies for joint clinical assessments. European Comission; 2024.

[76] Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews. Journal of Clinical Epidemiology. 2016;70:106-10.

[77] Khazaaleh S, Babar S, Alomari M, Imam Z, Chadalavada P, Gonzalez AJ, et al. Outcomes of total pancreatectomy with islet autotransplantation: A systematic review and meta-analysis. World J Transplant. 2023;13(1):10-24.

[78] Zhang YJ, Duan DD, Yuan H. Efficacy and safety of islet autotransplantation after total pancreatectomy in chronic pancreatitis: A systematic review and meta-analysis including 17 studies. Clin Res Hepatol Gastroenterol. 2020;44(4):598-608.

[79] National Health Service England. Clinical Commissioning Policy: Total pancreatectomy with islet auto transplant for chronic pancreatitis (adults). 2018.

[80] Gariani K, Peloso A, Galani V, Haidar F, Wassmer CH, Kumar R, et al. Effect of islet alone or islets after kidney transplantation on quality of life in type 1 diabetes: A systematic review. Transplant Rev (Orlando). 2024;38(4):100870.

[81] Kaviani M, Geramizadeh B, Karimzadeh S. Effectiveness of islet transplantation in diabetes mellitus type 1: a systematic review of the recent evidence. Minerva Endocrinol (Torino). 2025;50(1):113-9.

[82] Catarinella D, Melzi R, Mercalli A, Magistretti P, Tentori S, Gremizzi C, et al. Long-term outcomes of pancreatic islet transplantation alone in type 1 diabetes: a 20-year single-centre study in Italy. Lancet Diabetes Endocrinol. 2025.

[83] Marfil-Garza BA, Imes S, Verhoeff K, Hefler J, Lam A, Dajani K, et al. Pancreatic islet transplantation in type 1 diabetes: 20-year experience from a single-centre cohort in Canada. Lancet Diabetes Endocrinol. 2022;10(7):519-32.

[84] Rickels MR, Ballou CM, Foster NC, Alejandro R, Baidal DA, Bellin MD, et al. Islet Transplantation Versus Standard of Care for Type 1 Diabetes Complicated by Severe Hypoglycemia From the Collaborative Islet Transplant Registry and the T1D Exchange Registry. Diabetes Care. 2025.

[85] Lad SU, Ali KF, Johnston PC, San Martin VT, Bottino R, Lin YK, et al. Follow-Up of Patients After Total Pancreatectomy and Islet Cell Autotransplantation at Off-Site Islet Isolation Facility. J Clin Endocrinol Metab. 2023;108(6):1425-31.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Population 1 (patients with TPIAT): Results from three single-arm studies

Author, year	Greussner, 2014 [2]	Pollard, 2023 [1]	Coluzzi, 2023 [3]
Country	USA	UK	USA
Institution	Arizona Medical Center	Leicester General Hospital	Baylor University Medical Center
Funding	Not reported	None reported	Supported in part by an internal grant from the Baylor University Medical Center
Time period	August 2009 through August 2013	September 1994 and May 2011	31 March 2011 and 1 April 2021
Study design	NI	Long-term outcomes from a series of patients	Prospective observational study
Target group	Adults	Adults	Adults
Number of pts	61	60	166
Primary outcome	Transplantation outcomes	Not reported	Independent trends over time of the various scales and items of the EORTC QLQ-C30 and QLQ-PAN26
Intervention (I)	Robotic or open TPIAT	TPIAT	Total pancreatectomy with islet autotransplantation (TPIAT)
Patient selection for transplantation	Pts with CP	NR	Patient eligibility for TPIAT includes intractable pain despite previous medical treatment, detectable endogenous insulin secretion capacity evident by serum C-peptide, and the capacity to consent to the treatment. Pregnant women were not eligible for the surgical procedure.
Origin of islet cells	Autogenous	Autogenous	Autogenous
Transplantations, n	NR	NR	NR
Organ Procurement	Robot-assisted or open, not detailed	Islets were prepared and infused as previously described[27]. The pancreas was digested with Neutral Protease NB GMP Grade in combination with purified Collagenase NB 1 GMP Grade (SERVA Electrophoresis GmbH, Heidelberg, Germany). Unpurified whole pancreatic digest was suspended in M199	Islets were isolated by the modified Ricordi method, which has been previously described[28]. When the tissue volume (mL) exceeded 0.25 times body weight (kg), islets were purified with a COBE 2991 cell processor (Caridian BCT Inc., Lakewood, CO) using a density-adjusted iodixanol-based continuous density gradient. Endotoxin testing,

[27] https://pubmed.ncbi.nlm.nih.gov/12865792/

[28] Ricordi C, Lacy PE, Finke EH, Olack BJ, Scharp DW. Automated Method for Isolation of Human Pancreatic Islets. Diabetes (1988) 37(4):413–20. doi:10. 2337/diab.37.4.413 25. Matsumoto S, Noguchi H, Naziruddin B, Onaca N, Jackson A, Nobuyo H, et al. Improvement of Pancreatic Islet Cell Isolation for Transplantation. Proc (Bayl Univ Med Cent) (2007) 20(4):357–62. doi:10.1080/08998280.2007.11928323

Author, year	Greussner, 2014 [2]	Pollard, 2023 [1]	Coluzzi, 2023 [3]
Organ Procurement *(continuation)*		transplant media containing 20% human serum albumin. The islets were prepared while the surgeons completed the gastro-jejunostomy and choledochojejunostomy reconstruction.	gram staining, and bacterial and fungal cultures were performed on the final products as indicators of sterility.
Surgical Procedures	Not reported	The islets were infused into the portal vein via the middle colic vein or umbilical vein (after 1998) over 20-30 minutes. During the islet cell infusion portal vein pressures were continuously monitored to ensure they did not exceed 20 mmHg. The islet yield was converted into IEQ, with the diameter standardised to 150 µm. Islet viability in the final product was evaluated with fluorescein diacetate/propidium iodide staining.	All patients underwent total pancreatectomy with the surgical technique described previously[29], with or without splenectomy based on surgeon decision. Liberase MTF with Thermolysin MTF (Roche, Basel, Switzerland) or Collagenase NB with neutral proteases (SERVA Electrophoresis GMbH, Heidelberg, Germany) was infused into the pancreatic duct for digestion. Isolated islets were infused into the portal vein via the superior mesenteric vein with heparin (70 unit/kg body weight) while the patient was under general anesthesia. The portal vein pressure was regularly monitored during the islet infusion.
Immunosuppression	Not reported	Immediately prior to the islet cell infusion patients received 5,000 units of heparin intravenously. This has always been the policy in Leicester rather than heparin being included with the islets during the infusion (or 50% systemic and 50% with the islets in some units). The rational for the systemic heparinisation immediately prior to the islet cell infusion is to ensure that anticoagulation is adequate from the beginning of the infusion which is not possible in the early stages when heparin is included with the infusion.	Not reported
Type of pancreatectomy, n (%)	Total pancreatectomy: 52 (85) [robotic: 6 (12), open: 46 (88)], partial pancreatectomy: 1 (open, 100), completion pancreatectomy: 8 (open, 100)	Total: 57 (95.0) Partial: 3 (5.0)	NR
Diabetes before TPIAT (%)	NR	NR	12.1 %
Age at transplantation, yrs	Total: 42.2±1.6, robotic: 39±5.0, open: 42.5±1.6	44±11	41.1 (30.4-49.0)

[29] Shahbazov R, Yoshimatsu G, Haque WZ, Khan OS, Saracino G, Lawrence MC, et al. Clinical Effectiveness of a Pylorus-Preserving Procedure on Total Pancreatectomy With Islet Autotransplantation. Am J Surg (2017) 213(6): 1065–71. doi:10.1016/j.amjsurg.2016.09.051 21.
Yoshimatsu G, Shahbazov R, Saracino G, Lawrence MC, Kim PT, Onaca N, et al. The Impact of Allogenic Blood Transfusion on the Outcomes of Total Pancreatectomy With Islet Autotransplantation. Am J Surg (2017) 214(5): 849–55. doi:10.1016/j.amjsurg.2017.03.007 22.
Naziruddin B, Matsumoto S, Noguchi H, Takita M, Shimoda M, Fujita Y, et al. Improved Pancreatic Islet Isolation Outcome in Autologous Transplantation for Chronic Pancreatitis. Cel Transpl (2012) 21(2-3):553–8. doi:10.3727/096368911X605475 23.
Shahbazov R, Naziruddin B, Salam O, Saracino G, Levy MF, Beecherl E, et al. The Impact of Surgical Complications on the Outcome of Total Pancreatectomy With Islet Autotransplantation. Am J Surg (2020) 219(1): 99–105. doi:10.1016/j.amjsurg.2019.04.007

Author, year	Greussner, 2014 [2]	Pollard, 2023 [1]	Coluzzi, 2023 [3]
Female sex, n (%)	Total: 39 (62), robotic: 4 (67), open: 35 (64)	38 (63.0)	75 (65)
BMI, kg/m^2	Total: 26.6±0.91, robotic: 25.3±1.3, open: 26.8±1.0	22.7±4.5	26.3 (21.5-29.8)
Etiology of chronic pancreatitis, n (%)	Idiopathic (73%), hereditary (16%), alcohol-induced (11%)	Idiopathic: 43 (71.7) Alcohol: 11 (18.3) Gallstones: 3 (5.0) Pancreas divisum: 3 (5.0)	Alcoholic: 9 (7.8) Autoimmune: 7 (6.0) Hereditary: 19 (16) Idiopathic: 55 (47) Other: 26 (22)
Pancreatitis duration before transplantation, years	NR	NR	5.0 (3.0, 10.0)
Transplanted islet equivalent dose (IEQ/kg patient body weight)	Total: 3,048±461, robotic:2,592±680, open: 3,099±508	NR	5.1 (2.9-7.2) × 10^3
Follow-up after transplantation, yrs	2	10	78.8 months (range 9.4-125.5 months)
Patients for follow-up, n (%)	NR	10-year FU: 17 (28) Group 1 ("good response", G1): 5 Group 2 ("partial response", G2): 6 Group 3 ("poor" response", G3): 6	1-year FU: n=79 (68), 2-year FU: n=40 (34), 3-year FU: n=27 (13)
Outcomes			
Efficacy			
Glycaemic control			
HbA1c	NR	Baseline (n=60): 5.5 (4.4-9.7) After TPIAT subgroups : G1: maintained stable levels for up to ten years G2 vs. Group 1: á (**P<0.0003**) Group 3 vs. Group 1: á (**P<0.0001**)	HbA1c (%) Baseline (n=116): 6.0 (1.1) 1-year FU (n=79): 7.3 (2.0) 2-year FU (n=40): 7.3 (2.4) 3-year FU (n=27): 7.0 (1.4)
C-peptide secretion/OGTT	NR	Baseline (ng/mL, n=60): C-peptide 0 min:1.5 (0.2-5.9) C-peptide 30 min: 4.5 (0.8-13.6) C-peptide 120 min: 5.6 (1.0-12.5) **Mean C-peptide levels after OGTT vs. baseline:** G1**: s.s. á** 30 **(P=0.0006)** and 120 min **(P<0.0001)** G2: **s.s. á** 30 **(P=0.0066)** and 120 min **(P<0.0001)** G3: **s.s. á** 120 min **(p=0.0032)**	Serum C-peptide (ng/dL) Baseline (n=116): 1.8 (1.3) 1-year FU (n=79): 1.2 (1.2) 2-year FU (n=40): 1.4 (1.5) 3-year FU (n=27): 1.1 (1.3)

Author, year	Greussner, 2014 [2]	Pollard, 2023 [1]	Coluzzi, 2023 [3]
C-peptide secretion/OGTT *(continuation)*		**Mean C-peptide levels after OGTT between groups**: *G1 vs. G2:* Baseline: **s.s. á (P=0.0013)** 30 min: **s.s. á (P=0.0009)** 120 min: **s.s. á (P<0.0001)** *G1 vs. G3:* Baseline: **ss.s. á (P=0.0063)** 30 min: **s.s. á (P=0.0003)** 120 min: **s.s. á (P<0.0001)** *Glucose levels 30 and 2 hours after OGTT:* G1 vs. G2: **s.s. á (P<0.0001)** G1 vs. G3: **s.s. á (P<0.0001)**	
Fasting blood glucose	NR	NR	Fasting blood glucose (mg/dL): Baseline (n=116): 102 (29) 1-year FU (n=79): 152 (94) 2-year FU (n=40): 151 (65) 3-year FU (n=27): 124 (54)
Hypoglycaemia events/unawareness	NR	NR	NR
Insulin independence	Total: 14/61, robotic: 2/6, open: 12/55, 19% of patients became insulin-independent (after a range of 1-24 months)	G1: 29.4% (5/17) for 5 years and 17.6% (3/17) for > 10 years G2: 2 pts for 6 months after TPIAT G3: 2 pts > 10 years	Insulin dependence after TPIAT: 1-year FU: 78%, 2-year FU: 73%, 3-year FU: 71%
Exogenous insulin amount	Units of insulin: 27%: <10 units, 23% 11-25 units 31% >25 units	Insulin requirements: G1 (n=5): 100 % insulin-free for the first 5 years, and <10 units/day up to 10 years post-TPIAT G2 (n=6): <20 units/day Group 3: (n=6): >20 units/day	Exogenous insulin amount (unit/day): Baseline (n=116): 2.2 (8.0) 1-year FU (n=79): 14.7 (15.0) 2-year FU (n=40): 15.5 (15.9) 3-year FU (n=27): 14.4 (17.5)
Graft failure	NR	NR	NR
Pain management			
Pain score (SD)	**SF-36 pain score:** *Baseline:* total: 25.2±19.3, robotic: 38.4±19.2 open: 23.7±19.0 *1 month FU:* total: 34.7±18.8, robotic: 35.0±23.2, open: 34.6±18.6	NR	**Visual analogue scale:** Baseline n=116: 5.7 (2.1) 1-year FU n=79: 2.2 (2.9) 2-year FU n=40: 2.1 (2.8) 3-year FU n=27: 1.9 (2.6) Pain scores significantly decreased over time after TPIAT **(p<0.001)**

Author, year	Greussner, 2014 [2]	Pollard, 2023 [1]	Coluzzi, 2023 [3]
Pain score (SD)	*6 months FU:* total: 52.0±29.7, robotic: NR, open: 49.9±28.4 *1year-FU:* total: 57.4±25.7, robotic: NR, open: 57.4±25.7		
Pain drugs after intervention	*1-year FU:* 71% were pain-free and no longer required analgesics	NR	Morphine equivalent dose (mg/d): Baseline (n=116): 118 (137) 1-year FU (n=79): 44 (93) 2-year FU (n=40): 42 (68) 1-year FU (n=27): 35 (65) decreased over time **(p <0.001)**
Immunosupression	NR	NR	NR
Secondary complications of diabetes	NR	NR	NR
Cardiovascular disease	NR	NR	NR
Retinopahty	NR	NR	NR
Quality of life	NR	NR	**EORTC QLQ-C30 functioning scale,** 2-year FU, **s.s. á**: global health QoL **(p < 0.001)**, physical functioning **(p<0.001)**, role functioning **(p<0.001)**, emotional functioning **(p<0.001)**, cognitive functioning **(p=0.007)**, and social functioning **(p <0.001)** *Clinically relevant improvement* from baseline (≥10 points) in each functional scale domain of EORTC QLQ-C30. **EORTC QLQ-C30 symptom scales, s.s. â post-TPIAT**: fatigue **(p < 0.001)**, nausea and vomiting **(p<0.001)**, pain **(p<0.001)**, insomnia (p<0.001), appetite loss **(p = 0.001)**, and constipation **(p<0.001)** The reduction in these symptoms was also *clinically meaningful* (changes of ≥20 points) **EORTC QLQ-PAN26 symptom scales** pre- and post-TPIAT, **s.s. á over time**: pancreatic pain **(p <0.001)**, bloating **(p<0.001)**, digestive symptoms **(p<0.001)**, taste **(p= 0.009)**, indigestion **(p= 0.001)**, weight loss **(p<0.001)**, body image **(p= 0.003)**, and future worries **(p=0.009)** *Clinically meaningful reductions* in symptoms in all domains except flatulence, hepatic symptoms, and trouble with side effects **Functional scales in QLQ-PAN26,** after TPIAT**, s.s. á** : satisfaction with healthcare **(p = 0.004)** and sexuality **(p<0.001)**

Author, year	Greussner, 2014 [2]	Pollard, 2023 [1]	Coluzzi, 2023 [3]
Safety			
Overall complications, n (%)	NR	NR	NR
Major AE, n (%)	NR	NR	NR
Minor AE, n (%)	NR	NR	NR
Procedure-Related Complication rate	NR	NR	NR
Survival rate, %	100	16 died due to: ■ alcohol: 5, ■ heart disease: 1 ■ unknown: 7, ■ unrelated to surgery: 1, ■ natural causes: 1, ■ diabetes complication: 1	At 1, 2, and 3 years, 2, 6, and 9 patients had died (NI on the reasons why the patients died)
Procedure-related mortality, n (%)	Any in-hospital or 30-day mortality was observed	No patient died from complications related to their surgery	NR
Explantation	NR	NR	NR
Islet graft failure	NR	NR	NR
Length of stay, days	Total: 12.4±4.4, robotic: 13.2±1.9, open: 12.3±4.6	NR	NR

Abbreviations: AE … adverse event, C … control group, CP … chronic pancreatitis, EORTC QLQ-C30 … European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 survey, FU … follow-up, G … group, I … intervention group, IEQ … islet equivalent, n … number of patients, NI … no information, NR … not reported, n.s. … not significant, P … p-value, SD … standard deviation, pts … patients, QoL … Quality of life, QLQ-PAN26 … Quality of Life Questionnaire-pancreatic ductal adenocarcinoma-26, s.s. … statistically significant, TPIAT … total pancreatectomy with islet auto-transplantation, yrs … years

Table A-2: Population 2 (patients with islet and kidney transplantation) ICT vs Insulin Therapy: Results from one randomised controlled trial

Author, year	**Lablanche, 2018 [4]**
Country	France
Institution	15 University hospitals
Funding	Programme Hospitalier de Recherche Clinique grant from the French Government.
Time period	July 8, 2010, and July 29, 2013 (last follow up July 4, 2017)
Study design	Multicentre, open-label, randomised controlled trial
Target group	T1D
Number of pts	50
Primary outcome	β-score
Intervention (I)	Islet cell transplantation after kidney transplantation
Patient selection for implantation	Eligible patients were aged 18-65 years with T1D 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. Patients with T1D who had received a kidney graft were eligible for islet transplantation if they had a functional kidney graft 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
Origin of islet cells	Allogenic
Transplantations, n	NR
Organ Procurement	Pancreases were obtained from brain-dead, multi-organ donors procured through the Swiss Transplant Agency and the French Biomedicine Agency. 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.
Surgical Procedures	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.
Immunosuppression and other study treatments	The 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.
Comparator	Insulin therapy
Patient selection for comparator	Eligible patients were aged 18-65 years with T1D diagnosed at least 5 years previously and had basal and stimulated C-peptide concentrations of less than 0·1 nmol/mL.
Organ Procurement	NR
Surgical Procedures	Patients in the insulin group were treated with insulin for 6 months and registered on the islet transplantation waiting list. 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 HbA1c of less than 7% (58 mmol/mol) without severe hypoglycaemia.
Immunosuppression and other study treatments	NR
Age at transplantation, yrs	Total: 51 (41 to 58) I: 52 (40 to 57) C: 51 (42 to 58)
Female sex,n (%)	Total: 27 (57%) I: 12 (48%) C: 15 (68%)
BMI kg/m^2	Total: 23·7 (21·9 to 25·5), I: 22·9 (21·9 to 25·5), C: 23·9 (22·2 to 25·5)
Diabetes duration before transplantation, years	Total: 30 (24 to 38), I: 34 (25 to 41), C: 30 (24 to 37)

Author, year	Lablanche, 2018 [4]
Severe hypoglycemia	Severe glycaemic lability (with severe hypoglycemia): Total: 36 (77%) I: 18 (72%) C: 18 (82)
Transplanted islet equivalent dose (IEQ/kg patient body weight)	Total: 320,667 (265,842-387,897 I: 320,667 (259,445-426,511) C: 327,993 (273,417-377,200)
Follow-up after transplantation, yrs	Median follow-up 184 days
Patients for follow-up, n (%)	NR
Outcomes	
Efficacy	
Glycaemic control	
HbA1c	**Median modified ß-score:** *Baseline vs. after 6-months:* **I: s.s. á:** 0 (0-2) vs. 6 (5-7), **p<0·0001** 16 (64% [95% CI 43-82])/25 pts had a modified β-score of 6 or higher 8 (32% [15-54])/25 pts had a modified β-score between 3 and 5 **C: s.s. á**: 0 (IQR 0-1) vs 1.5 (0.0-2.0), **p=0.0091**, 0 (0% [0-15])/22 had a modified β-score of 6 or higher (**p<0.0001**). 3 (14% [3-35])/22 pts had a score between 3 and 5 **12 months after the first infusion vs. baseline**: 29 (63% [95% CI 48-77])/46 pts had a modified β-score of 6 or higher (**p<0·0001**); the median modified β-score was 7 (5-8; **p<0·0001**) ***Median HbA1c 12 months after first infusion vs. baseline*** 43 pts: 5·8% (IQR 5·5-6·7; **p<0·0001**), ***Between group:*** HbA1c **s.s.â** in I vs. C at 6 months (5·6% [38 mmol/mol] vs 8·2% [66 mmol/mol], **p<0·0001**)
C-peptide secretion/OGTT	NR
Fasting blood glucose	**Fasting blood glucose:** n.s. difference between groups: I: 5.9 (IQR 5·2-6.7) vs. C: 5.7 (4.9-10.9) (p=0.92) **HbA1c of less than 7% without severe hypoglycaemia:** *I vs. C* 21 (84% [95% CI 64-96]) vs. 0 (0% [0-15], **p<0·0001** *After Transplant vs. Baseline* 32 (70% [95% CI 54-82])/46 pts vs. 1 (2% [0-11])/47 pts (**p<0·0001**) 37 (80% [66-91])/46 pts had reached an HbA1c of less than 7%
Hypoglycaemia events/unawareness	***Median number of severe hypoglycaemic events per year**, I vs. C:* 0 (IQR 0-0) vs. 2 (0-4), **p<0·0001** ***Median number of non-severe hypoglycaemic events**, I vs. C:* 0 (0-0) vs. 5 (1-17), **p=0.0003** ***Free of severe hypoglycaemia**, I vs. C:* 23 (92% [95% CI 74-99]) vs. 8 (36% [17-59]), **p<0.0001** ***Median number of severe hypoglycaemic events per year**, 12 months FU vs. baseline:* I: 0 (IQR 0-0) vs. 2 (0-4), **p<0·0001** ***Median number of non-severe hypoglycaemic events that the patient was aware of**,* *12 months FU vs. baseline:* 0 (0-0) vs. 10 (4-17), **p<0·0001** ***Free of severe hypoglycemia**, 12 months FU vs baseline:* 39 (85% [95% CI 71-94])/46 vs. 16 (34% [21-49])/47, **p<0·0001**
Insulin independence	***Insulin independence**, 6 months FU:* I: 11 (44% [24-65])/25 pts (p=0·0004)
Exogenous insulin amount	NR
Graft failure	43 (93% [82-99])/46 pts had a functioning graft
Kidney graft survival	GFR (ml/min), baseline vs. 12 months FU: I: 90.5 [76.6-94] vs. 71.8 [59-89], **p=0.0008;** C: 63 [55-71] vs. 57 [45.5-65.1], **p=0.014**
Kidney function, renal allograft function	NR

Author, year	Lablanche, 2018 [4]
Pain management	
Pain score (SD)	NR
Pain drugs after intervention	NR
Immunosupression	NR
Secondary complications of diabetes	NR
Cardiovascular disease	NR
Retinopathy	NR
Quality of life	**SF-36 questionnaire,** 6 month FU, I vs. C: **s.s. á** in gain in general health perceptions (**p=0.008**) and health transition (**p<0.001**)
Safety	
Overall complications, n (%)	NR
Major AE, n (%)	SAEs occurred in > 4 pts [n/47 pts (% of pts with this event)] **Infections and infestations:** 20 in 20 pts (42.6%), most occurred: *acute pylenoephritis*: 2 (4.3) 0-6 m FU **Gastrointestinal disorder:** 19 in 18 (38.3%), most occurred: *vomiting*: 6 in 6 pts (12.8): 5 (0-6 m FU), 1 (6-12 m FU), d*iarrhea*: 5 in 4 pts (8.5): 4 (0-6 m FU), 1 (6-12 m FU) **Blood and lymphatic system disorders:** 17 in 16 pts (34 %), most occurred: *leukopenia*: 5 in 3 pts (6.4): 5 (0-6 m FU), *neutropenia*: 5 in 5 pts (10.6): 4 (0-6 months FU), 1 (6-12 m FU) **Cardiac disorders:** 5 in 5 pts (10.6%), on waiting list: *fatal cardiac arrest:* 1 (2.1), *myocarditis*: 1 (2.1); 0-6 months FU: *transient cardiac arrest*: 1 (2.1), *atrial fibrillation*: 1 (2.1), *tachycardia paroxysmal*: 1 (2.1) **General disorders and administration site conditions**: 7 in 6 pts (12.8%), most occured: *hyperthermia*: 3 in 2 pts (4.3), 2 (on waiting list), 1 (0-6 m FU) **Immune system disorders:** 6 in 6 pts (12.8%), most occurred: transplant rejection: 4 in 4 pts (8.5): 4 (0-6 m FU) **Investigations:** 5 in 5 pts (10.6%) **Metabolism and nutrition disorders:** 8 in 6 pts (12.8%) **Musculoskeletal and connective tissue disorders:** 5 in 5 pts (10.6%) **Nervous system disorders:** 8 in 8 pts (17.0%) **Renal and urinary disorders:** 7 in 6 pts (12.8) **Respiratory, thoracic, and mediastinal disorders:** 5 in 4 pts (8.5%)
Minor AE, n (%)	NR
Procedure-related AE	■ 9 in 9 pts (19.1%) 0-6 months FU: Post-procedural haemorrhage: 1 (2.1%) ■ Hepatic haematoma: 1 (2.1%) ■ Traumatic haemothorax: 1 (2.1%) ■ Postoperative renal failure: 1 (2.1%) ■ Post procedural haematoma: 1 (2.1%) ■ Arterial injury: 1 (2.1%) ■ Subcutaneous haematoma: 1 (2.1%) ■ Peritoneal heamarrhage: 1 (2.1%)
Survival rate, %	NR
Explantation	NR
Islet graft failure	NR
Length of stay, days	NR

Abbreviations: AE- adverse event, ATG … antithymocyte globulin, C … control group, eGFR … Estimated Glomerular Filtration Rate, EORTC QLQ-C30 … European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 survey, FU … follow-up, HbA1c … haemoglobin A1C, I … intervention group, IAK … islet after kidney, IEQ … islet equivalent, IQR … interquartile range, n … number of patients, NI … no information, NR … not reported, n.s. … not significant, P … p-value, SD … Standard deviation, pts … patients, QoL … Quality of life, s.s. … statistically significant, T1D … Type 1 diabetes, US … United States, yrs … years

Table A-3: Population 2: ICT with kidney transplant vs ICT alone (patients with T1D and kidney transplant): Results from 1 NRSI

Author, year	**Rickels, 2022 [5]**
Country	US
Institution	Various
Funding	The long-term analyses were supported by JDRF grant 1-SRA-2019-728-A-N (to L.G.H. and M.R.R.). Study conduct was supported by National Institute of Diabetes and Digestive and Kidney Diseases grants to the University of Pennsylvania (U01DK070430), University of Iowa (U01DK070431), University of Miami (U01DK070460), and University of California, San Francisco (U01DK085531), and National Institute of Allergy and Infectious Diseases grants to the University of Alberta (U01AI065191), Uppsala University (U01AI065192), University of Minnesota (U01AI065193), Northwestern University (U01AI089316), and Emory University (U01AI089317). In addition, the study was supported in part by National Center for Research Resources and National Center for Advancing Translational Sciences grants to Emory University (UL1TR000454), Northwestern University (UL1RR025741 and UL1TR000150), University of California, San Francisco (UL1TR000004), University of Illinois, Chicago (UL1TR000050), University of Miami (UL1TR000460), University of Minnesota (M01RR000400 and UL1TR000114), and University of Pennsylvania (M01RR00040 and UL1TR000003)
Time period	2010-2017
Study design	Prospective interventional and observational cohort study
Target group	T1D
Number of pts	72
Primary outcome	Graft function
Intervention (I)	Islet-Alone
Patient selection for implantation	Participants who completed the U.S. Food and Drug Administration-registered phase 3 CIT Consortium islet-alone (n = 48) (CIT-07) (2) or islet-after-kidney (n = 24) (CIT-06) (3) transplantation studies with continued PHPI graft function were invited to enroll in the extended followup study (CIT-08). Subjects who participated in phase 2 CIT Consortium isleta lone studies (CIT-02, CIT-03, CIT-04, or CIT-05) could also enroll in CIT-08 but were not included in the long-term analysis of the phase 3 studies
Origin of islet cells	Allogenic, single deceased donor derived
Transplantations, n	1-3 per patient
Organ Procurement	For immunosuppression we followed the methodology first described by Hering et al.. (6) for islet-alone transplants, modified for islet-after-kidney transplants to allow substitution of mycophenolate mofetil for sirolimus and cyclosporine for tacrolimus if already used for the kidney transplant.
Surgical Procedures	Each subject received an initial intraportal infusion of a PHPI product containing $5,000 islet equivalents (IEQ)/kg body wt of recipient manufactured from a single deceased donor pancreas as previously described. Individuals who remained insulin dependent after 75 (islet-alone) or 30 (islet-after-kidney) days from receiving an initial PHPI product could receive one or two additional PHPI products each containing $4,000 IEQ/kg body wt within 240 days of the initial transplant.
Immunosuppression and other study treatments	NR
Comparator	Islet (with kidney transplant)
Patient selection for comparator	As above
Organ Procurement	NR
Surgical Procedures	NR
Immunosuppression and other study treatments	NR
Age at transplantation, yrs	Age (years) I: 47.8±11.5 C: 51.8±11.1
Female sex,n (%)	I: 29 (60) C: 11 (46)
BMI kg/m^2	I: 24.9±3.1 C:24.6±3.1
Diabetes duration before transplantation, years	I:31.5±11.0 C: 37.0±10.0 P= 0.04
Severe hypoglycemia	NR

Author, year	Rickels, 2022 [5]
Transplanted islet equivalent dose (IEQ/kg patient body weight)	I: 11,278±3,935 C: 12,585±6,191 P= 0.77
Follow-up after transplantation, yrs	2-3
Patients for follow-up, n (%)	Failed: I=7, C=9 Withdrew with function: I=15, C=7 Completed with function: I=26, C=8
Outcomes	
Efficacy	
Glycaemic control	
HbA1c	The median of the mean pretransplant HbA1c levels : 7.2% (Range: 6.6%-9.3%) Day 28 post-first PHPI transplant to PHPI failure or end of follow-up (n=18): 6.3% (Range: 5.5%-7.7%) Median change in HbA1c: -1.1% (range: -2.7% to +0.7%) **HbA1c <7.0%:** Day 75: I: 42/48 (87.5%) C:17/24 (71%) **HbA1c <6.5%** Day 75: **I:** 41/48 (85%) C:13/24 (54%) I: 49% maintained functioning grafts with HbA1c <7.0% over time, but none had levels <6.5% at the end of maximal follow-up at 8.3 years. C: 35% maintained islet graft function with HbA1c <7.0% (**P= 0.0017** vs. islet-alone) and 17% with HbA1c <6.5% (**P< 0.0001** vs. islet-alone) at the end of maximal followup at 7.3 years. With use of Bayesian joint analysis, the modeled evolution of HbA1c in the islet-alone and islet-afterkidney study cohorts demonstrated an initial decline from medians of 7.4% and 7.9% to 5.7% and 6.0%, respectively, that gradually rose to 6.7% and 7.8% over 8 years. Thus, the projected median benefit of PHPI transplantation for glycemic control lasts >8 years for both islet-alone and islet-after-kidney recipients
C-peptide secretion/OGTT	I: Mean fasting C-peptide rose over the first 1 post-transplant year from undetectable levels to a peak of 1.7 ng/mL, fell to 1.3 ng/mL at 3 years, then more slowly to a mean of 1.2 ng/mL at the median follow-up of 5.6 years and 1.0 at 8 years. C: Mean fasting C-peptide rose over the first 1.2 post-transplant 4 years from undetectable levels to a peak of 2.0 ng/mL, and fell more rapidly to 1.5 ng/mL at the median IAK follow-up of 3.3 years and 0.7 ng/mL at the end of follow-up at 7.1 years. The higher fasting C-peptides in C than I subjects probably reflects the lower post-kidney-transplant eGFR of the IAK subjects.
Fasting blood glucose	NR
Hypoglycaemia events/unawareness	A total of 12 severe hypoglycemia episodes occurred in five subjects (7% [3 islet-alone and 2 islet-after-kidney]) over the course of the primary studies. There were no additional severe hypoglycemia episodes during the long-term follow-up study in any subject with islet graft function (Fig. 3A).
Insulin independence	53 of 72 pts (74% [37 of 48 islet-alone and 16 of 24 islet-afterkidney]) achieved a period of insulin independence with HbA1c maintained at <7.0%, n.s. between groups Insulin independet after infusion: 1 infusion: 20 pts (37.66%) 2 infusions: 30 (56.66%) 3 infusions: 3 (5.66%) 30 pts (57%) remained insulin independent throughout their duration of follow-up (20 of 37 isletalone and 10 of 16 islet-after-kidney), n.s difference between groups Among those who achieved insulin independence at any time, 44% are projected to remain insulin independent for up to 8 years.
Exogenous insulin amount	Median of the means of pretransplant daily insulin dose: 32.1 units/day (Range: 17.4-53.7 units/day). 28 post-first PHPI transplant to PHPI failure or end of follow-up in these subjects: 17.5 units/day (Range: 8.2-33.3 units/day). The median drop in daily insulin dose was 54% (range: 81% drop to 34% increase). 23 subjects that achieved insulin independence had to restart daily insulin, but with retained PHPI graft function

Author, year	Rickels, 2022 [5]
Graft failure	I: 56% actuarial survival of islet graft function at maximum follow-up time of 8.3 years C: 49% actuarial survival at maximum follow-up time of 7.3 years (**P=0.004**)
Kidney graft survival	eGFR declined by 6.9 mL/min/1.73 m^2 during the 1st year posttransplant in I and by only 0.7 mL/min/1.73 m^2 in C 1st to up to 8 years: the slope of eGFR was only 1.27 mL/min/1.73 m^2/year in the islet-alone cohort and was in fact positive in the islet-after-kidney cohort IAK subjects had a relatively consistent rate of improvement in eGFR over their course with little evident change in eGFR during the first year following initial PHPI transplant
Kidney function, renal allograft function	NR
Pain management	
Pain score (SD)	NR
Pain drugs after intervention	NR
Immunosupression	NR
Secondary complications of diabetes	NR
Cardiovascular disease	No major pre- to posttransplant changes in cardiovascular risk factors
Retinopahty	NR
Quality of life	NR
Safety	
Overall complications, n (%)	104 SAEs occurred I: 71, C: 33 I: 71 SAEs in 27/48 subjects, 36 SAEs in primary study, 35 in long-term follow-up, during 226 total years of follow-up, 101 in the primary study, and 125 in long-term follow-up C: 33 SAEs in 15/24 subjects, 29 SAEs in base study, 4 in long-term follow-up, during 77 total years of follow-up, 66 in the Base study, and 11 in long-term follow-up study)
Major AE, n (%)	Events unrelated to protocol directed therapy I: 37 ■ episode of atrial fibrillation following hip fracture: 1 ■ gastrointestinal: 3 (small bowed obstruction x2 in 1 subject, gastroparesis) ■ episodes of non-cardiac chest pain: 4 ■ infections: 5 (pneumonia, gastroenteritis x2, appendicitis, urinary infection) ■ food allergy: 1 ■ injuries: 5 (hip fractures x3, vertebral fracture, post collision hepatic hematoma) ■ episodes of severe hypoglycemic events: 4 ■ malignancies: 2 (breast cancer, prostate cancer) ■ cerebrovascular (cerebellar stroke): 1 ■ non-vascular neurological: 4 (hydrocephalus x2 in one subject, dementia, convulsion) ■ psychiatric (delusion, schizophrenia, suicide attempt, conversion syndrome): 4 ■ renal (renal atheromatous emboli, acute kidney injury): 2 ■ medication error: 1 C: 15 ■ infection (osteomyelitis, cellulitis X2): 3 ■ gastrointestinal: 3 (gastrointestinal haemorrhage x2, gastroparesis) ■ ophthalmologic episode: 1 (vitreous haemorrhage) ■ other: 3 (drug allergy, fever, impaired healing) ■ hypoglycaemia: 2 ■ neurological events: 3 (transient ischemic attack, neuropathy X2) ■ small intestinal carcinoma resectable: 1
Minor AE, n (%)	NR
Procedure-related AE	0
Survival rate, %	100

Author, year	Rickels, 2022 [5]
Explantation	A list of islet donor-specific alloantibodies that appeared during the primary studies and affected 2 of 48 islet-alone and 5 of 24 islet-after-kidney One additional islet-alone recipient developed islet donor-specific alloantibodies at 3 years, with islet graft failure occurring 5 years following initial PHPI transplant. One islet-alone subject developed islet donor-specific alloantibodies following graft failure and cessation of immunosuppression. There were no additional de novo islet or kidney donor-specific alloantibodies in islet-after-kidney recipients during extended follow-up and no episodes of kidney rejection in any of the islet-after-kidney recipients
Islet graft failure	56% actuarial survival of islet graft function at maximum follow-up time of 8.3 years, Islet-after-kidney recipients had 49% actuarial survival at their maximum follow-up time of 7.3 years (p = 0.004) Failed: I: 7 C: 9
Length of stay, days	NR

Abbreviations: AE- adverse event, ATG … antithymocyte globulin, C … control group, eGFR … Estimated Glomerular Filtration Rate, EORTC QLQ-C30 … European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 survey, FU … follow-up, HbA1c … haemoglobin A1C, I … intervention group, IAK … islet after kidney, IEQ … islet equivalent, IQR … interquartile range, n … number of patients, NI … no information, NR … not reported, n.s. … not significant, P … p-value, SD … Standard deviation, pts … patients, QoL … Quality of life, s.s. … statistically significant, T1D … Type 1 diabetes, US … United States, yrs … years

Table A-4: Population 2 (patients with T1D and kidney transplant) ICT vs insulin therapy: Results from 1 NRSIs

Author, year	Vantyghem, 2009 [8]
Country	France
Institution	NR
Funding	French Ministry of Health (PHRC 2000), The Conseil Re´gional Nord-Pas de Calais (FEDER), and The Inter Regional Research Fund G4 (Amiens Caen Lille Rouen)
Time period	NR
Study design	Nonrandomised study, cohort
Target group	T1D
Number of pts	30
Primary outcome	NR
Intervention (I)	Islet cell transplantation (n=13, 6 islet after kidney and 7 islet transplantation alone)
Patient selection for implantation	Islet transplantation alone was proposed to patients with hypoglycemia unawareness or diabetes lability, if subcutaneous pump had been refused or had failed. Exclusion criteria were as follows: age 18 to 65 years, diabetes duration more than 5 years, body mass index (BMI) less than 28 kg/m^2, blood creatinine level less than 250 mg/dL, albuminuria below 300 mg/day, and no desire for pregnancy (13). Islet after kidney transplan tation was proposed when patients were ineligible for kidney-pancreas transplantation (i.e., patients older than 45 years, or with severe macroangiopathy) if creatinine blood level was stable at least 6 months after kidney transplantation and steroid discontinuation
Origin of islet cells	Allogenic
Transplantations, n	1 or 2 subsequent islet grafts within 3 months until at least 10,000 islets equivalent/kg of body mass were transplanted
Organ Procurement	Pancreata were harvested by our team during standard multiorgan procurement and were processed within 8 hr from procurement. Islets were isolated with a slightly modified standard automated method as previously described[30] using purified collagenase, before undergoing isopycnic purification in Biocoll (Biochrom AG Berlin, Germany) gradients with a cell separator (Cobe 2991; Gambro BCT, Lakewood CO). Once an islet preparation isolated from a donor was deemed suitable for trans-plantation (i.e., containing >250,000 islet equivalents or >4000 islet equivalent/kg, viability >80%, and volume >8 mL), the recipient was admitted for surgical or radiologic implantation of a silicone catheter in the portal tree under general anesthesia.

[30] Ricordi C, Lacy PE, Finke EH, et al. Automated method for isolation of human pancreatic islets. Diabetes 1988; 37: 413.

Author, year	Vantyghem, 2009 [8]
Surgical Procedures	The delay between kidney and islet transplantation ranged between 15 and 30 months.
Immunosuppression and other study treatments	Immunosuppressive treatment included induction by antiinterleukin receptor type 2 (daclizumab, Roche, Fontenay/Bois, France), and indefinite administration of sirolimus (Wyeth, Puteaux, France) and low doses of tacrolimus (Fujisawa, France). Continuous immunosuppression according to the Edmonton protocol.
Comparator	Intraperitoneal Insulin Infusion, n=17
Patient selection for comparator	Patients with type 1 diabetes followed-up in the same center and treated with IPII according to the guidelines of the French collaborative group EVADIAC. Briefly, indications for IPII are type 1 diabetes with Hb1Ac levels above 7%, despite frequent and appropriate self blood monitoring and insulin dose adapting, because of unreliable subcutaneous insulin absorption; patients with type 1 diabetes treated with intensive subcutaneous insulin therapy by multi-injections or most often ambulatory pump who obtain an Hb1Ac level below 7% at the expense of hypoglycemia or brittleness with unpredictable hyper and hypoglycemia altering the quality of life. Age, BMI, and kidney function were not exclusion criteria
Organ Procurement	Not relevant
Surgical Procedures	The pump (Implantable Model 2001 or 2007; Minimed Technologies, Sylmar CA) was implanted under the abdominal wall after general anesthesia and its silicon-coated polysulfone catheter was inserted in the peritoneal cavity. The infused insulin was Hoechst's 21 pH neutral semisynthetic human insulin (Hoechst, Frankfurt, Germany) at a concentration of 400 IU/mL and stabilised by a glycol-poly-ethylenepolypropylene surface-active agent (Genapol; Hoechst). The pump was refilled under aseptic conditions every 6 weeks.
Immunosuppression and other study treatments	NR
Age at transplantation, yrs	I: 43.1±6.2 C: 40.0±7.7
Female sex,n (%)	I: 7 (54) C: 12 (71)
BMI kg/m^2	NR
Diabetes duration before transplantation, years	I: 25.3±8.7 C: 23.3±11.9
Severe hypoglycemia	Per week: I: 2.6±2.1 C: 2.9±2.2
Transplanted islet equivalent dose (IEQ/kg patient body weight)	<10,000
Follow-up after transplantation, yrs	3
Patients for follow-up, n (%)	NR
Outcomes	
Efficacy	
Glycaemic control	
HbA1c	Baseline vs … … 1-year FU: I: 8.2±1.1 vs. 6.1±0.7 (**P<0.001**) C: 8.4±1.8 vs. 7.9±1.0 (**P<0.01**) … 2-year FU: I: 8.2±1.1 vs. 6.4±1.0 (P<**0.001**) C: 8.4±1.8 vs. 7.5±0.8 (**P<0.01**) … 3-year FU: I: 8.2±1.1 vs. 6.6±1.1 (**P<0.01**) C: 8.4±1.8 vs. 8.1±1.3 (n.s) **Between groups I vs. C:** 1-year FU 6.1±0.7 vs. 7.9±1.0 (P<**0.0001**) 2-year FU 6.4±1.0 vs. 7.5±0.8 **(P<0.01)** 3-year FU 6.6±1.1 vs. 8.1±1.3 **(P<0.01)**

Author, year	Vantyghem, 2009 [8]
C-peptide secretion/OGTT	36 months FU: 11/13 patients from I had a blood C-peptide level <0.2 ng/mL
Fasting blood glucose	**Mean blood glucose (mmol/L):** Baseline vs … … *1-year FU:* I: 12.2±3.0 vs. 6.6±1.1, **(P<0.001)** C: 9.3±3.1 vs. 8.8±2.0, (n.s) … *2-year FU:* I: 12.2±3.0 vs. 6.8±1.3, **(P<0.001)** C: 9.3±3.1 vs. 8.7±2.6, (n.s.) … *3-year FU:* I: 12.2±3.0 vs. 7.1±1.6, **(P<0.01)** C: 9.3±3.1 vs. 9.0±1.5, (n.s.) ***Between groups, I vs. C:*** *1-year FU* 6.6±1.1±8.8±2.0, **(P<0.05)** 6.8±1.3±8.7±2.6 (P=0.05) 7.1±1.6 vs. 9.0±1.5, **(P<0.05)** Mean glycemia differences: 24 months FU: n.s. differences 36 months FU: **s.s. â (P<0.05)** in I vs C.
Hypoglycaemia events/unawareness	Per week Baseline vs … … *1-year FU :* I: 2.6±2.1 vs. 0.3±0.5, (**P<0.001**) C: 2.9±2.2 vs. 1.6±1.6 (n.s.) … *2-year FU:* I: 2.6±2.1 vs. 0.2±0.5, (**P<0.001**) C: 2.9±2.2 vs. 1.5±1.2 (n.s.) … *3-year FU:* I: 2.6±2.1 vs. 0.7±1.1, (**P<0.01**) C: 2.9±2.2 vs. 1.7±1.8, (n.s) Between groups, I vs. C: *1-year FU:* 0.3±0.5 vs. .6±1.6, (**P<0.01**) *2-year FU:* 0.2±0.5 vs. 1.5±1.2, (**P<0.01**) *3-year FU:* 0.7±1.1 vs. 1.7±1.8, (n.s.)
Insulin independence	*6 months FU:* 9/13 patients were insulin-free (3/6 islet-after-kidney and 6/7 islet transplantation alone) *12 months FU:* 10/13 pts were insulin free 24 months FU: 7/13 pts were insulin free 36 months FU: 6/13 pts were insulin free
Exogenous insulin amount	**Daily insulin need (IU/d)** Baseline vs. … … 1-year FU: I: 46±12 vs. 4.4±8.5 **(P<0.001)** C: 43±18 vs. 43±20 (n.s.) … 2-year FU I: 46±12 vs. 10±14 (**P<0.001)** C: 43±18 vs. 45±20 (n.s.) … 3-year FU I: 46±12 vs. 12±16 (**P<0.001)** C: 43±18 vs. 46±19 (n.s.)

Author, year	Vantyghem, 2009 [8]
Exogenous insulin amount *(continuation)*	***Between groups, I vs. C:*** 1-year FU: 4.4±8.5 vs. 43±20 **(P<0.0001)** 2-year FU: 10±14 vs. 45±20 **(P<0.0001)** 3-year FU: 12±16 vs. 46±19 (P<0.0001) *At 6 and 12 months FU*: daily insulin need was **s.s. â** in the I than in the C group
Graft failure	Primary islet graft function was confirmed in all 13 patients, as demonstrated by mean plasma C-peptide levels at 3 months of 1.5±0.7 (normal range, 0.5-2 ng/mL) and individual fasting values greater than 0.5 ng/mL.
Kidney graft survival	NR
Kidney function, renal allograft function	NR
Pain management	
Pain score (SD)	NR
Pain drugs after intervention	NR
Immunosupression	NR
Secondary complications of diabetes	NR
Cardiovascular disease	NR
Retinopahty	NR
Quality of life	NR
Safety	
Overall complications, n (%)	NR
Major AE, n (%)	**1-year FU:** *Intervention:* Number of major AE/patient: 1.38 (18/13) *Grade 3 AE: 17,* Elevated liver enzymes (1), neutropenia (4), dysautonomia decompensation (2), proteinuria (1), infection (1), anaemia (1), diarrhoea (1), dyspnoea (1), weight loss (1), dermatosis (1), aphtosis (1), liver hematoma (1), vitreous body bleeding (1) *Grade 4 AE: 1,* Choleperitonitis (1) *Control:* Number of major AE/patient: 0.76 (13/17) *Grade 3 AE: 10,* Glucose imbalance (4), abdominal pain (5), pump dysfunction (3) *Grade 4 AE: 1* Infection/pump explanation (1) **2-year FU:** *Intervention:* *Grade 3 AE: 8,* NR *Grade 4 AE: 0* *Control:* *Grade 3 AE: 0* *Grade 4 AE: 0* **3-year FU:** *Intervention:* *Grade 3 AE: 3,* NR *Grade 4 AE: 0* *Control:* *Grade 3 AE: 2,* NR *Grade 4 AE: 0*

Author, year	Vantyghem, 2009 [8]
Minor AE, n (%)	1-year FU: Intervention: Number of minor AE/patient: 3.84 (50/13) Grade 1 AE: 27, Diarrhea (5), abdominal pain (1), dermatosis (2), weight loss (5), elevated serum creatinine (1), infections (5), leg edema (3), proteinuria (1), anemia (1), dysfunctional uterine bleeding (1), ovarian cysts (2) Grade 2 AE: 23, phtosis (8), proteinuria (1), puncture failure (1), anemia (2), dermatosis (3), stress gastritis (1), infections (3), diarrhea (3), daclizumab intolerance (1) Control: Number of minor AE/patient: 0.47 (8/17) Grade 1 AE: 5, Abdominal pain (2), Pump dysfunction (3) Grade 2 AE: 3, Glucose imbalance (1), Pouch problem (2) 2-year FU: Intervention: Grade 1 AE: 10, NR Grade 2 AE: 13, NR Control: Grade 1 AE: 7, NR Grade 2 AE: 1, NR 3-year FU: Intervention: Grade 1 AE: 7, NR Grade 2 AE: 6, NR Control: Grade 1 AE: 2, NR Grade 2 AE, 2 NR 1-year FU: most grade 1 and 2, were fourfold á with I vs. C (5.2 vs. 1.2 AE/patient per year) During 2 & 3-years FU: the number of AE progressively â (by half each year) in both groups but remained fourfold higher in the I than C
Procedure-related AE	NR
Survival rate, %	NR
Explantation	Pump explanation: 1
Islet graft failure	NR
Length of stay, days	NR

Abbreviations: AE … adverse event, C … control group, EORTC QLQ-C30 … European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 survey, FU … follow-up, HbA1c … hemoglobin A1C, I … intervention group, IEQ … islet equivalent, IQR … interquartile range, n … number of patients, NI … no information, NR … not reported, n.s. … not significant, P … p-value, SD … Standard deviation, pts … patients, QoL … Quality of life, s.s. … statistically significant, T1D … Type 1 diabetes, US … United States, yrs … years

Table A-5: Population 2 (patients with T1D and kidney transplant) ICT with kidney transplant: Results from three single-arm studies

Author, year	Vantyghem, 2012 [9]	Markmann, 2020 [7]	Vantyghem, 2019 [6]
Country	France	US	France
Institution	Institut National de la Sante´ et de la Recherche Me´dicale Unite´ 859	10 centres in North America	NR
Funding	Grants from the 7th Framework Program of the European Commission (ß-Cell Therapy), the French Ministry of Health (PHRC 2001), Fond Europe´en de Developpement Re´gional, Conseil Re´gional Nord Pas de Calais, Groupement Inter Hospitalier G4 (Amiens, Caen, Lille, Rouen), and Agence Nationale de La Recherche (ANR-10-LABX-46).	National Institutes of Health	French Ministry of Health, Programme Hospitalier de Recherche Clinique 2001, the European Community (Fond Europeen de ´ Developpement R ´ egional), Conseil R ´ egional du ´ Nord-Pas-de-Calais, Programme d'Investissements d'Avenir Labex European Genomic Institute for Diabetes (ANR-10-LABX-46), Societ´ e Francophone ´ du Diabete, Soci ` et´ e Française d ´ 'Endocrinologie, Association de Recherche pour le Diabete, ` Santelys, and Agence de la Biomedecine
Time period	May 2003 and December 2007	April 8, 2010 until November 17, 2017	13 March 2003 and 1 December 2012
Study design	A single-arm open-labeled study with a 3-yr follow-up in a referral center	Pivotal phase 3, prospective, open-label, single-arm study	Observational, prospective, parallel arm, cohort
Target group	T1D	T1D after kidney transplant	T1D
Number of pts	23	24	28
Primary outcome	Graft function and β-score	Freedom from severe hypoglycemic events and HbA1c ≤ 6.5% or reduced by ≥ 1 percentage point at 1 year posttransplant	Exogenous insulin, graft function
Intervention (I)	Islet-Alone and Islet-After-Kidney Transplantation	Islet after kidney-transplant	Islet-Alone and islet with kidney transplantation transplantation
Patient selection for implantation	Participants in two clinical trials exploring the outcome of IT using the Edmonton immunosuppression protocol in nonuremic patients with labile type 1 diabetes (brittle diabetes)	18-68 years at the time of enrollment, T1D for ≥5 years, stable kidney transplant, absent stimulated C-peptide, IAH as determined by Clarke score, and a history of SHEs in the prior 12 months despite medical care provided by an endocrinologist or diabetologist. Alternatively, when not meeting the hypo-glycemia criterion, a subject could meet inclusion criteria if his or her HbA1c was ≥7.5% after having received ≥12 months of prospectively followed intensive insulin therapy.	Enrolled subjects had type 1 diabetes documented for 5 years at the time of islet transplantation and arginine stimulated C-peptide ,0.3 ng/mL. Nonuremic patients had hypoglycemia unawareness and/or documented metabolic lability and an estimated glomerular filtration rate (eGFR) .60 mL/min/1.73 m^2 Uremic patients had a kidney graft with stable renal function, no episodes of kidney graft rejection, and blood pressure in the normal range whatever the use of antihypertensive drugs
Origin of islet cells	Allogenic	Allogenic, purified human pancreatic islets (PHPI)	Allogenic
Transplantations, n	2 infusions: 10 3 infusions: 13	1 PHPI infusion: 11 2 PHPI infusion: 11 3 PHPI infusions: 2	Total: 74 islet infusions 2 or 3 infusions within 68 days (43-91) per patient
Organ Procurement	NR	PHPI were manufactured at 10 manufacturing facilities, each associated with that clinical site. The CIT-defined manufacturing process used a common master production batch record, including standardised lot release criteria, process controls, test methods, and organ donor acceptance criteria. Pancreata from deceased donors 15-65 years of age were processed within 12 hours of retrieval. Donor exclusion criteria included history of diabetes, HbA1c > 6% (42 mmol/mol), and donation after cardiac death	Islet transplantation consisted of up to three sequential islet infusions within 3 months

Author, year	Vantyghem, 2012 [9]	Markmann, 2020 [7]	Vantyghem, 2019 [6]
Surgical Procedures	NR	Each PHPI lot (dose), containing > 5000 islet equivalents (IEQ)/kg for the first dose and ≥ 4000 IEQ/kg for subsequent doses (if any), was prepared from a single pancreas and was transplanted by portal vein infusion. Access to the portal vein was achieved percutaneously or by minilaparotomy (30 and 9 infusions, respectively). Subjects who were not insulin independent at 30 days after the first or second dose were eligible for a subsequent infusion until 8 months after the initial transplant. This left a 4-month posttransplant interval for stabilization before assessment of the primary endpoint.	The access to the portal vein was gained under general anaesthesia by percutaneous catheterization of a peripheral portal branch under ultrasound guidance or by surgical catheterization of a small mesenteric vein. In all cases, heparin (35 units/kg) was added to the final islet preparation, gently infused by gravity with portal pressure monitoring.
Immunosuppression and other study treatments	Edmonton immunosuppression protocol	Induction immunosuppression consisted of rabbit antithymocyte globulin (ATG) and etanercept1for the first transplant, with basiliximab replacing ATG at subsequent transplants and in a single case of suspected sensitivity to ATG. The calcineurin-based maintenance immunosuppression regimen used for the renal transplant was continued after the islet transplant.	Immunosuppression consisted of tacrolimus target trough levels at 3-6 ng/mL, and sirolimus, target trough levels at 12-15 ng/mL for 3 months and at 7-10 ng/mL the 1st year and 5-6 ng/mL thereafter. A five-dose induction course of daclizumab (1 mg/kg) was administered biweekly beginning 1 h before the first infusion. For IAK, the median (interquartile range) elapsed time between kidney and islet transplantation was 22 months (18-38). When an islet preparation was available, a course of anti-interleukin-2 receptor antibody was performed, repeated for each of the two or three islet injections performed over 3 months
Comparator	NR	NR	Islet cell transplantation with kidney transplantation
Patient selection for comparator	NR	NR	See above
Organ Procurement	NR	NR	As above
Surgical Procedures	NR	NR	Islet transplantation protocols as described above. The kidney transplantation had been performed with a standard-of-care protocol, i.e., in most cases anti-thymocyte antibodies, mycophenolate, and tacrolimus with an initial bolus of 1 g of prednisolone. Steroids had been progressively tapered over 3-9 months until complete discontinuation if there was no sign of kidney rejection. About 12 months after kidney transplantation, mycophenolate was progressively switched to sirolimus to reach blood trough sirolimus levels of 7-10 ng/mL and tacrolimus levels around 5 ng/mL. The blood pressure and renal function had to be normal.
Immunosuppression and other study treatments	NR	NR	A comprehensive clinical and biological evaluation was performed before islet transplantation and each year after the first islet infusion, with intermediate routine clinical visits at least twice per year. Daily exogenous insulin requirements, antidiabetic treatments, and adverse events were recorded at each visit. Exogenous insulin was reintroduced when A1C increased above 6.5% (48 mmol/mol) on two consecutive measurements. The following parameters were analyzed using standardised methods unless otherwise indicated: daily glucose profile (mean glucose, SD around mean glucose, and percentage of time spent in

Author, year	Vantyghem, 2012 [9]	Markmann, 2020 [7]	Vantyghem, 2019 [6]
Immunosuppression and other study treatments *(continuation)*			hypoglycemia ,70 mg/dL) assessed with continuous glucose monitoring (CGM) for three consecutive days, fasting and postprandial blood glucose and C-peptide (RIA-coat C-peptide; Mallinckrodt, Paris, France) (detection threshold 0.2 ng/mL), plasma creatinine, A1C, and tacrolimus and sirolimus trough levels. The presence and type of autoantibodies GAD, islet cell antibody (ICA), and IA2 were evaluated before transplantation, after each islet infusion, yearly during the follow-up, and, in case of graft loss, 3 months after discontinuation of immunosuppression
Age at transplantation, yrs	44 (median) 37-52 IQR	median IQR age was 52.7 (29.2-69.6)	All: 43 (37-50) I: 42 (36-51) C: 44 (40-49)
Female sex,n (%)	12 (52)	11 (46)	MALE SEX All: 13 (46) I: 7 (50) C: 6 (43)
BMI kg/m^2	NR	24.0 (18.9-30.4)	All: 22.9 (21.3-24.6) I: 24.6 (22.9-25.9) C: 22.6 (20.2-22.9)
Diabetes duration before transplantation, years	28 yr (IQR 23-34)	36.5 (17-55)	NR
Severe hypoglycemia	NR	6.0 (0.0-30.0)	No. of severe hypoglycemia events in previous year: All: 2 (1-5) I: 3 (1-7) C: 2 (0-3)
Transplanted islet equivalent dose (IEQ/kg patient body weight)	12,615 (IQR 10,933-15,606)	11,345 (5,168-28,393)	All:13,45 (10.93-15.28) I: 12,07 (10.64-14.65) C: 13,83 (12.79-15.43)
Follow-up after transplantation, yrs	3	1 year (365 days), 2 years (730 days), 3 years (1,095 days)	10 years
Patients for follow-up, n (%)	24 (100%)	1 subject was lost to follow-up at day 849 and 1 subject withdrew consent at day 1174 after transplant.	1-year FU: 28 (100) 5-year FU: 27 (94); 10-year FU: 20 (71)
Outcomes			
Efficacy			
Glycaemic control			
HbA1c	Baseline 8.3 (7.3-9) vs … … 6 month FU: 6.0 (5.7-6.4), **P<0.01** … 36 month FU: 6.7 (5.9-7.7), **P<0.01**	***Primary outcome:*** *$HbA_{1c} \leq 6.5\%$ or a reduction in HbA1c of ≥1 point in the absence of experiencing SHEs, n (%)* 1 year FU: 15 subjects (62.5%; **P < .001**), 2 year FU: 14 (58.3%; **P = .0012**); 3 year FU: 11 (45.8%; P = .0369; *Key secondary endpoint: $HbA_{1c} < 7.0\%$ in the absence of experiencing SHEs, n (%)* 1 year FU: 15 (62.5%) 2 year FU: 14 (58.3%); 3 year FU: 10 (41.7%)	**Glycated hemoglobin (%):** 1-year FU: 5.9 (5.5-6.7), **p<0.0001**; 5-year FU: 6.9 (6.1-7.5), **p<0.0001;** 10-year FU: 6.7 (6.1-8), **p=0.0009**; **Mmol/mol:** 1-year FU: 41 (37-50) 5-year FU: 52 (43-58) 10-year FU: 50 (43-64)

Author, year	Vantyghem, 2012 [9]	Markmann, 2020 [7]	Vantyghem, 2019 [6]
HbA1c *(continuation)*		*HbA1c: baseline 8.1% [7.0%-9.3%] vs. FU*: 1 year FU: 6.0% [5.3%-6.4%], **P < .001**; 2-year FU: 6.3% [5.5%-6.7%], P = .002; 3-year FU:6.3% [5.5%-6.9%], **P < .001**; ***HbA1c ≤ 6.5%, n (%)*** 1-year FU: 15 (62.5%), 2-year FU: 12 (50.0%), 3-year FU: 9 (37.5%)	
C-peptide secretion/OGTT	NR	C-peptide was undetectable in all subjects before transplant 1-year FU: 1.8 (1.6-2.5) ng/mL 2-year FU: 1.8 (1.5-2.1) ng/mL 3-year FU: 1.3 (0.8-1.6) ng/mL *60 minutes postmeal ingestion, ng/mL:* 1-year FU: 5.2 (3.6-7.7) 2-year FU: 4.4 (2.7-5.1) 3-year FU: 4.4 (1.2-8.2) **P≤0.001** for all comparisons vs. baseline *90 minutes post-meal ingestion, ng/mL:* 1-year FU: 5.5 (4.1-6.7) 2-year FU: 4.0 (3.6-6.8) 3-year FU: 4.4 (1.3-7.2) **P<0.001** for all comparisons vs baseline	NR
Fasting blood glucose	NR	*Fasting glucose mg/dl vs. Baseline 147.5 [92.5-162.5]:* 1-year FU: 109.0 [101.0-115.0], P = .036 2-year FU: 112.0 [99.5-127.0], P = .175 3-year FU: 111.0 [99.00-127.0], P = .334 *Mean glucose mg/dL vs. baseline: 189.0 [147.0-213.0] mg/dL* 1-year FU: 113.0 [109.0- 133.0], 2-year FU: 130.0 [108.0-145.0], 3-year FU: 121.0 [105.5- 152.0], **P≤0.0625** for all comparisons to baseline *Glucose SD, baseline 72.0 [61.0-80.0] mg/dl) vs.* 1-year FU: 20.0 [16.0-30.0], 2-year FU: 21.0 [17.0- 31.0], 3-year FU: 25.5 [13.5-51.5] **P≤0.0625** for all comparisons to baseline	**Mean glucose (mg/dL), p-value vs. baseline:** 1-year FU: 112 (102-133), **p<0.0001**; 5-year FU: 126 (110-144), **p<0.0001**; 10-year FU: 118 (113-154), **p=0.0007**
Hypoglycaemia events/unawareness	% time in hypoglycaemia, n=23 Baseline: 5 (1- 8) vs … … 6 months FU: 0 (0-3.5), **p<0.05** … 36 months FU: 0 (0-2), **p<0.05**	*SHEs were eliminated posttransplant in* 1-year FU: 19 (79.2%), **P=0.003**; 2-year FU: 18 (75.0%), P =0.**011**; 3-year FU: 15 (62.5%), P =0.154	Number of severe hypoglycaemia events in previous year p-value vs. baseline: 1-year FU: 0 (0-0), **p<0.0001;** 5-year FU: 0 (0-0), **p<0.0001;** 10 years FU: 0 (0-0), **p<0.0001**
Insulin independence	Insulin requirement, n=23: Baseline: 0.63 (0.40-0.75) vs … … 6 months: 0 (0-0), **P<0.01** … 36 months: 0 (0-0.28, **P<0.01**	1-year FU: 9 (37.5%), P = 0.036**;** 2-year FU: 7 (29.2%), P =0.189; 3-year FU: 4 (16.7%), P =0.736;	NR

Author, year	Vantyghem, 2012 [9]	Markmann, 2020 [7]	Vantyghem, 2019 [6]
Exogenous insulin amount	NR	*Baseline: 0.50 [0.39-0.58] units kg−1 d−1 vs.* 1-year FU: 0.0 [0.0-0.01], **P<0.001** 2-year FU: 0.00 [0.0-0.22], **P<0.001** 3-year FU: 0.00 [0.00-0.26], **P=0.002**	**Exogenous insulin requirements (IU/kg per day),** p-value vs. baseline**:** 1-year FU: 0 (0-0.04), **p<0.0001;** 5-year FU: 0 (0-0.36), **p<0.0001;** 10-year FU: 0.28 (0-0.43) **p<0.0001**
Graft failure	NR	NR	6 pts
Kidney graft survival	NR	NR	**EGFR mL/min/1.73 m^2,** p-value vs. baseline**:** 1-year FU: 68 (55-81), n.s. 5-year FU: 64 (51-80), n.s. 10-year FU: 54 (43-91), n.s.
Kidney function, renal allograft function	NR	**Median eGFR (mL/min/1.73 m^2):** Baseline, n=24: 82 (56-86) vs. 75-day FU, n=21: 70 [52-83] mL/min/1.73 m^2, â **P<0.001;** 1-year FU, n=19: 73 (58-92), P=0.568 2-year FU: 76 (63-88), P=0.268; 3-year FU: 78 (66-88), P=0.583	NR
Pain management			
Pain score (SD)	NR	NR	NR
Pain drugs after intervention	NR	NR	NR
Immunosupression	NR	NR	NR
Secondary complications of diabetes	NR		NR
Cardiovascular disease	NR	NR	NR
Retinopahty	NR	NR	NR
Quality of life	NR	*Diabetes Distress score* *Baseline: 2.3 [1.7-3.1] vs.* 75-day FU: 1.8 [1.7-2.8], **P=0.002**, 1-year FU: 1.5 [1.3-1.9], **P= 0.006**, 2-year FU: 1.6 [1.2-1.8], **P=0.019**, 3-year FU: 1.7 [1.1-2.4], **P=0.008** *Fear of hypoglycemia (HFS score)* *Baseline: 2.0 [1.7-2.4] vs.* 75-day FU: 1.3 [0.96- 1.9], **P<0.001** 1-year FU: 0.74 [0.0-1.74], **P=0.002** 2-year FU: 0.41 [0.0- 1.6], P = .039 3-year FU: 0.6 [0.0-1.7]; P = .047 Trend toward less fear of hypoglycemia in subjects who were insulin independent vs insulin dependent EuroQOL Visual Analog Scale: Baseline vs. 1-year FU: 79.0 (75.0-82.0, **P < .001**) 2-year FU: 80.0 (74.0-85.0, P = .095) 3-year FU:: 78.0 (70.0-85.5, P = .033)	NR

Author, year	Vantyghem, 2012 [9]	Markmann, 2020 [7]	Vantyghem, 2019 [6]
Safety			
Overall complications, n (%)	NR	Total Adverse Events: 509	**1st year, SAEs:** ■ Related to infusion procedure: 11, ■ Related to immunosuppression: 5 ■ Diabetes complication: 1 **1-10 years FU, SAEs**: ■ Related to immunosuppression: 8 ■ Diabetes-related: 11
Major AE, n (%)	NR	***Grade 3: Severe adverse events: 83*** (most occurred): ■ Hypoglycaemia: 21 ■ Hypoglycemia unconsciousness: 5 ■ Urinary tract infection bacterial:4 ***Grade 4: Life Threatening or Disabling Adverse events: 12*** ■ Hypoglycaemic unconsciousness: 4 ■ Neutropenia: 2 ■ Blindness cortical: 1 ■ Cardiac arrest: 1 ■ Hypoglycaemia: 1 ■ Hypoglycaemic seizure: 1 ■ Osteomyelitis acute: 1 ■ Post-transplant lymphoproliferative disorder: 1 All subject recipients SAEs from induction immunosuppression initiation through day 365 posttransplant and day 1095 after final transplant, 13 SAEs were related or possibly related to immunosuppression treatment.	**First year:** *Immunosuppression related SAEs:* ■ Non-opportunistic infections: 2 ■ Haematological disorders (leukopenia..):1 ■ Diarrhea: 2 *Diabetes complications related:* ■ Aputations: Toe: 1 **1 to 10 years post IT:** *Immunosuppression related:* ■ Basal carcinoma: 2 ■ Sqamous cell skin carcinoma: 2 ■ Non-opportunistic infection: 2 ■ Opportunistic infection: 2 *Diabetes complications related:* ■ Myocardial infarct: 1 ■ Acute pulmonary oedema: 1
Minor AE, n (%)	NR	***Grade 1: Mild adverse events: 317*** (most occurred): ■ Blood magnesium decreased: 36 ■ Haemoglobin decreased: 32 ■ Blood sodium decreased: 18 ■ Blood bicarbonate decreased: 16 ■ Aspartate aminotransferase increased: 11 ***Grade 2: Moderate adverse events: 97*** (most occurred): ■ Haemoglobin decreased: 8 ■ Urinary tract infection bacterial: 7 ■ Blood phosphorus decreased: 6 ■ Hypoglycaemia: 6 ■ Blood albumin decreased: 5 ■ Vomiting: 5	NR

Author, year	Vantyghem, 2012 [9]	Markmann, 2020 [7]	Vantyghem, 2019 [6]
Procedure-related AE	NR	No procedure-related bleeding events were associated with the 39 PHPI infusions.	**First year SAE procedure-related:** 11 ■ Biliary peritonitis: 1 ■ Biliary tract bleeding: 1 ■ Arteriovenous fistula: 1 ■ Liver hematoma: 1 ■ Partial portal vein thrombosis: 1 ■ Moderate hemoperitoneum: 1 ■ Intestinal occlusion: 1 ■ Functional occlusion: 1 ■ Abdominal wall hematoma: 3
Survival rate, %	NR	100	NR
Explantation	NR	No patients experienced renal allograft rejection.	NR
Islet graft failure	NR	6 pts experienced islet graft failure	6 pts lost graft function Kaplan-Meier estimates of graft survival in the entire study group: 5-years: 82% (95% CI 62-92), 10-years: 78% (57-89)
Length of stay, days	NR	NR	NR

Abbreviations: AE … adverse event, C … control group, EORTC QLQ-C30 … European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 survey, FU … follow-up, I … intervention group, IEQ … islet equivalent, IQR … interquartile range, n … number of patients, NI … no information, NR … not reported, n.s. … not significant, P … p-value, statistical significance , SD … Standard deviation, pts … patients, QoL … Quality of life, s.s. … statistically significant, yrs … years

Table A-6: Population 3 (patients with T1D) ICT vs pancreas transplant : Results from 1 NRSI

Author, year	**Maffi, 2011 [10]**
Country	Italy
Institution	Diabetes Research Institute, San Raffaele Scientific Institute,
Funding	NR
Time period	Between 1999 and 2010
Study design	Observational (prospective?)
Target group	Adults (8-64) T1D
Number of pts	66
Primary outcome	Clinical outcomes and adverse events
Intervention (I)	Islet cell transplantation
Patient selection for transplantation	■ age 18 to 64 years; ■ duration of type 1 diabetes >5 years; ■ no measurable levels of stimulated Cpeptide; ■ body weight <75 kg for males, <70 kg for females; ■ reduced hypoglycemia awareness; ■ instable metabolic control with severe hypoglycemia or ketoacidosis leading to hosptalization, despite intensive insulin management; ■ progression of retinopathy and neuropathy, despite intensive insulin management; ■ serum creatinine <1.5 mg/dl, and urinary protein excretion <300 mg/dl; ■ cardiovascular disease excluding the patient from being listed for pancreas transplantation
Origin of islet cells	Allogenic (donor, not specified)
Transplantations, n	9 patients received a single infusion, 16 patients two infusions, and 8 three infusions for a total of 57 infusions
Organ Procurement	NR
Surgical Procedures	Islets were infused in the liver under local anesthesia through the percutaneous transhepatic puncture of the portal vein under ultrasound guide.
Immunosuppression and other study treatments	TA patients were treated according to different immunosuppressive regimens: ■ Edmonton: daclizumab; chronic therapy with sirolimus and low doses tacrolimus (trough levels 4 ng/ml) (12 patients) ■ Pre-transplant treatment with sirolimus before the first islet infusion and Edmonton protocol thereafter (10 patients) ■ ATG for 4 days; chronic therapy with sirolimus and MMF (3 patients) – Pre-transplant treatment with sirolimus; ATG for 4 days; chronic therapy with sirolimus and MMF (8 patients)
Comparator	Pancreas transplantation
Patient selection for comparator	■ age 18 to 64 years; ■ duration of type 1 diabetes >5 years; ■ clinical and emotional problems, with insufficient exogenous insulin therapy; ■ history of frequent and severe acute metabolic complications (hypoglycemia, hyperglycemia, ketoacidosis) which required hospitalization, despite intensive insulin management; ■ rapid progression of neuropathy and/or retinopathy during the previous year; ■ serum creatinine <1.5 mg/dl, regardless of urinary protein excretion.
(Organ) Procurement	NR
Surgical Procedures	PTA was performed with the enteric diversion of exocrine secretion in all cases (all detail provided)
Immunosuppression and other study treatments	PTA patients received ATG (7 days) and steroids (methylprednisolone bolus at induction; prednisone 10 mg per day for 6 months). Chronic imunosuppression included mycophenolate mofetil (MMF), cyclosporine (8 cases), and MMF and tacrolimus (25 cases).
Age at transplantation, yrs	I: 36±8.6 C: 37±8.4
Female sex,n (%)	I: 15 (45.4) C: 14 (42.2)
BMI kg/m^2	NR
Diabetes duration before transplantation, years	I: 23±8.6 C: 23±9.9

Author, year	Maffi, 2011 [10]
Severe hypoglycemia events, 1 year pretransplant	Hypoglycemia unawareness: I: 33 (100) C: 33 (100)
Transplanted islet equivalent dose (IEQ/kg patient body weight)	Not reported
Follow-up after transplantation, yrs	>1
Patients for follow-up, n (%)	100 %
Outcomes	
Efficacy	
Glycaemic control	
HbA1c	NR
C-peptide secretion, OGTT	NR
Fasting blood glucose	NR
Hypoglycaemia events/unawareness	NR
Insulin independence	Insulin independence: I: 19 out of 33 (57%) C: 25 out of 33 patients (76 %)
Exogenous insulin amount	NR
Graft function	NR
Kidney function	NR
Pain management	
Pain score (SD)	NR
Pain drugs after intervention	NR
Immunosupression	NR
Secondary complications of diabetes	
Cardiovascular disease	NR
Retinopahty	NR
Quality of life	NR
Safety	
Overall complications, n (%)	NR
Major AE, n (%)	NR
Minor AE, n (%)	Adverse events I vs. C CMV reactivation: 2 vs. 21 (p<0.001) Other infections: 2 vs. 5 ■ Urinary tract infection: 0 vs. 3 ■ Bacterial sepsis: 0 vs. 2 Necrotizing fasciitis: 0 vs. 1 Worsening kidney function: 5 vs. 4 ■ End-stage RD: 1 vs. 2 ■ Worsened DN: 1 vs. 3 ■ Resolved after TW: 2 vs. 0 Other medical complications: ■ Thrombotic TP: 0 vs. 1 ■ Toxic hepatitis: 1 vs. 0 TAC-ind. Optic neuritis: 0 vs. 1

Author, year	Maffi, 2011 [10]
Procedure-Related Complication rate	I vs. C RBC transfusion: 2 vs.14 Relaptarotomy: 0 vs. 18 Transplantectomy: NA vs. 12 Thrombisis (total): 3 vs. 13 ■ Medical therapy: 3 vs. 4 ■ Fogarty: NA vs. 2 ■ Transplectomy: NA vs. 7 Bleeding (total): 12 vs. 5 ■ Medical therapy: 2 vs. 2 ■ Surgical revision: NA vs. 2 ■ Transplanctectomy: NA vs. 1 Acute rejection (total): 9 ■ Transplantectomy: NR vs. 4 ■ Medical therapy: NA vs. 4 Chronic rejection: NR vs. 1
Survival rate, %	NR
Procedure-related mortality, n (%)	NR
Explantation	NR
Islet graft feailure	I: early failure (i.e., exhaustion of C-peptide secretion within 4 weeks): 5 partial islet function: 9 (27 %) C: peri-operative removal of the graft due to surgical complications (considered early failures): 7 (21%)
Length of stay, days	I: 16 (9-19) C:19 (16-24) P=0.009

Abbreviations: AE … adverse event, C … control group, EORTC QLQ-C30 … European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 survey, FU … follow-up, HbA1c … haemoglobin A1C, I … intervention group, IEQ … islet equivalent, n … number of patients, NI … no information, NR … not reported, n.s. … not significant, P … p-value, pts … patient, QoL … Quality of life, SD … Standard deviation, s.s. … statistically significant, T1D … type 1 diabetes,

Table A-7: Population 3 (patients with T1D) ICT: Results from 2 single-arm studies

Author, year	Shapiro, 2006 [11]	Hering, 2016 [12]
Country	Canada	USA
Institution	9 sites, six in North America and three in Europe	8 centers in North America
Funding	Supported by a grant (NIS01) from the Immune Tolerance Network.	-
Time period	Not defined	NR
Study design	Single-group, phase 1-2 trial	Multicenter, single-arm, phase 3 study
Target group	T1D	Type 1 Diabetes complicated by severe hypoglycemia
Number of pts	36	48
Primary outcome	Isulin independence with adequate glycemic control 1 year after the final transplantation.	Achievement of an HbA1c level of <7.0% (53 mmol/mol)
Intervention (I)	Islet transplantation	Islet cell transplantation
Patient selection for transplantation	Eligible subjects were: ■ between the ages of 18 and 65 years, ■ had undetectable C-peptide levels, ■ type 1 diabetes mellitus for more than 5 years with recurrent neuroglycopenia, including reduced awareness of their hypoglycaemic episodes or severe glycaemic lability. ■ To confirm eligibility, an endocrinologist or diabetologist assessed subjects independently of the islet-transplantation team. Appropriate attempts to optimise intensive insulin therapy and glycaemic monitoring had failed in all subjects.	Inclusion criteria included the following: ■ age 18-65 years, ■ T1D for >5 years, ■ absent stimulated C-peptide, IAH and/or marked glycemic lability, ■ and a history of SHEs in the prior 12 months despite medical care provided by an endocrinologist or diabetologist, who asserted that the candidate had been adherent with respect to office visits (three or more in the preceding 12 months), self-monitoring of blood glucose levels (three or more times daily), and the use of an insulin pump or administration of three or more injections of insulin daily as prescribed
Origin of islet cells	Allogenic, brain dead multiorgan donors	Allogenic (donor, not specified)
Transplantations, n	Total: 77 11 (31%) pts: 1 infusion 9 (25%) pts: 2 infusions 16 (44%) pts: 3 infusions	1-3 per pts, Total: 75 infusions: 1 infusion: 22 (45.8%), 2 infusions: 25 (52.1%), 3 infusions: 1 subject (2.0%)
Organ Procurement	Islets were prepared locally in Good Manufacturing Practice-grade facilities at each of the nine sites, according to identical standard operating procedures. The pancreas was distended by controlled ductal perfusion with the use of common batch lots of Liberase human islet enzyme (Roche Diagnostics), previously validated at the participating sites. The pancreas was digested in a Ricordi chamber and purified on continuous Ficoll gradients on a cooled apheresis system (model 2991, Cobe Laboratories). The islets were then washed and resuspended in transplant medium (Mediatech), and the manufactured islet-cell product was infused into the portal vein without culture within 2 hours after completion of the isolation and purification.	PHPI were manufactured at the transplant site. The CIT-defined good manufacturing practice process included standardised lot release criteria and test methods. Pancreata from deceased donors 15-65 years of age were processed within 12 h of procurement.
Surgical Procedures	A cumulative islet mass of 10,000 islet equivalents per kilogram or more was delivered with at least two islet infusions, unless insulin independence was achieved with a single transplant. A third islet infusion was offered if circulating C peptide was detectable and insulin independence was not achieved after two infusions. The percutaneous transhepatic approach for portal venous access was used in all cases, with Doppler ultrasonography performed on days 1 and 7 after transplantation.	Each PHPI lot (dose), containing 5,000 islet equivalents (IEQ)/kg for the first dose and $4,000 IEQ/kg for subsequent doses (if any), was prepared from a single pancreas and was transplanted by portal vein infusion. Access to the portal vein was achieved per-cutaneously or by minilaparotomy. Subjects who were not insulin independent at 75 days after the first dose, or 30 days after a second dose, were eligible for a subsequent infusion until 8 months after the initial transplant. This left a 4-month interval for stabilization prior to assessment of the primary end point.

Author, year	Shapiro, 2006 [11]	Hering, 2016 [12]
Immunosuppression and other study treatments	The immunosuppressive regimen was based on that previously described in the Edmonton protocol.4 Five doses of daclizumab at a dose of 1 mg per kilogram were administered intravenously over a period of 8 weeks after each transplantation. Sirolimus was administered once daily to achieve a target trough therapeutic range of 12 to 15 ng per milliliter for 3 months after transplantation, after which the target trough range was lowered to 7 to 12 ng per milliliter. Tacrolimus was administeredtwice daily and adjusted to achieve a target trough level of 3 to 6 ng per milliliter.	Induction immunosuppression consisted of rabbit anti-thymocyte globulin and etanercept for the first transplant, with basiliximab replacing rabbit anti-thymocyte globulin at subsequent transplants. Sirolimus and low-dose tacrolimus were used for maintenance immunosuppression.
Comparator	NR	NR
Patient selection for comparator	NR	NR
(Organ) Procurement	NR	NR
Surgical Procedures	NR	NR
Immunosuppression and other study treatments	NR	NR
Age at transplantation, yrs	30-59	48.4 (26.2-65.5)
Female sex,n (%)	NR	29 (60)
BMI kg/m^2	19-25	25.1 (18.9-29.8)
Diabetes duration before transplantation, years	11-51	25.1 (18.9-29.8)
Severe hypoglycemia events, 1 year pretransplant	NR	6.5 (0-336)
Transplanted islet equivalent dose (IEQ/kg patient body weight)	5,006	11,972 IEQ/kg (range 5,227-25,553)
Follow-up after transplantation, yrs	41 (37-50) months	2
Patients for follow-up, n (%)	I: while on the waiting list: 99 (100), after the first infusion: 75 (76), after completion of a full islet transplant: 1 month: 77 (78), 3 months: 70 (71), 6 months: 70 (71), 12 months: 65 (66), 24 months: 53 (54), 36 months: 45 (46)	1-year FU: 3 (6%) %) were nonevaluable for the primary end point 2-year FU: 5 (17%) withdrew consent (imputed failures in the study)
Outcomes		
Efficacy		
Glycaemic control		
HbA1c	NR	**HbA1c level of ≤6.5% (48 mmol/mol)** *1 year FU* 38/48 (71%), vs. baseline (**P<0.001**) *2-year FU:* 33/48, vs. baseline (**P=0.02**)

Author, year	Shapiro, 2006 [11]	Hering, 2016 [12]
HbA1c *(continuation)*		**HbA1c level <7.0% (53 mmol/mol):** Baseline vs. 75 day-FU: 40% vs. 87.5%, **P<0.0003** Baseline vs. 1-year FU: 40% vs. 87.5%, **P<0.0003** Baseline vs. 2-year FU: **Median HbA1c levels:** â from 7.2% (55 mmol/mol) at baseline to 5.9% (41 mmol/mol) and 5.6% (38 mmol/mol) at days 75 and 365, respectively (**P<0.0003**).
C-peptide secretion, OGTT	C-peptide secretion ≥0.3 ng per milliliter: 2-year-FU in 70% of pts	C-peptide levels á and glucose levels âin response to a MMTT (**P<0.0003**)
Fasting blood glucose	NR	NR
Hypoglycaemia events/unawareness	All subjects with residual islet function were completely protected from severe hypoglycemic episodes, as reported from days 28 to 365 after transplantation	**Eradication of SHEs with excellent glycemic control; HbA1c level ≤7% [53 mmol/mol]):** *1 year FU vs. baseline*: 42/48 pts (87.5%), vs. baseline, **P<0.001** *2 year FU:* 34/48 (71%), vs. baseline, **P<0.01** All subjects had experienced at least one SHE in the year prior to enrollment; only 2 of 45 evaluable subjects reported SHEs in the year after islet transplantation (**P<0.0003**).
Insulin independence	Insulin-independent 1-year FU: 16 (44%, 5 with one transplant, 6 with two transplants, and 5 with three transplants) 2-year FU: 6 (17%) 3-yer FU: 1 (5%)	Insulin independence: 75-day-FU: **23%** 1-year-FU: **52.1%** Among 25 subjects who were insulin independent at 1 year, 13 received one islet infusion, and 12 received two islet infusions. As of day 730, the median interval without exogenous insulin among the 25 subjects was 684 consecutive days (range 210-720); 20/48 enrolled pts (42%) remained insulin independent at 2-year FU
Exogenous insulin amount	NR	**Median insulin use**: â 0.49 units/kg at baseline to 0.13 units/kg at day 75 and 0.00 units/kg at day 365 (range 0.00-0.43) (**P <0.0003**)
Graft function	10 subjects (28%) had complete graft loss: primary nonfunction: 4, early graft loss: 2 withdrew from further treatment: 4	**Functioning islet graft** (defined as a basal or stimulated serum C-peptide level >0.3 ng/mL): 75-day FU: 95% 1-year FU: 94%
Kidney function	In terms of renal function, a modest decline in creatinine clearance with a mild elevation in serum creatinine levels was observed over time, which was associated in some cases with increased albuminuria	median GFR â: *Baseline* 102 mL/min/1.73 m^2 (range 80-130) *vs. 75-day FU:* 98 mL/min/1.73 m^2, (P=0.09, range 42-140), *vs. 1-year FU:* to 90 mL/min/1.73 m^2, (**P=0.0008** vs. baseline, range 59-129). *vs. >2 years, n=35:* 82 mL/min/1.73 m^2 (**P<0.0001** range 54-123)

Author, year	Shapiro, 2006 [11]	Hering, 2016 [12]
Pain management		
Pain score (SD)	NR	NR
Pain drugs after intervention	NR	NR
Immunosupression	NR	NR
Secondary complications of diabetes		
Cardiovascular disease	None occured	NR
Retinopahty	None occured	NR
Quality of life	NR	NR
Safety		
Overall complications, n (%)	NR	NR
Major AE, n (%)	***Serious immunosuppression-related events included:*** ■ Neutropenia (five cases), ■ pneumonia, ■ mouth ulcers, ■ gastrointestinal conditions (two cases), ■ fever, ■ chest pain, ■ pericardial effusion, ■ pyelonephritis, ■ worsening genital herpes, and ■ appendiceal abscess.	*1-year FU: 30 in 21 pts* 22 attributed to the transplant procedure and/or immunosuppression and 8 to nonstudy causes, most common number of events (n of pts): ■ Febrile neutropenia: 3 (2) ■ Neutropenia 3 (2) ■ Vomiting: 2 (2) ■ Non cardiac chest pain: 2 (2) ■ Gastroenteritis: 2 (2) ■ Post procedural complication: 2 (2) ■ Post procedural haemorrhage: 2 (2) There were no SAEs related to access by mini-laparotomy (19 procedures). *2-year FU: 8;* 2 infections, 6 nonstudy causes: ■ Chest discomfort: 1 ■ Food allergy: 1 ■ Pneumocystis jiroveci pneumonia: 1 ■ Pyelonephritis: 1 ■ Hip fracture: 1 ■ Hypoglycaemic unconsciousness: 1 ■ Dementia: 1
Minor AE, n (%)	***10 most common minor AE were:*** mouth ulceration (in 92% of subjects), ■ anemia (81%), ■ leukopenia (75%), ■ diarrhea (64%), ■ headache (56%), ■ neutropenia (53%), ■ nausea (50%), ■ vomiting (42%), ■ acne (39%), ■ and fatigue (39%).	NR

Author, year	Shapiro, 2006 [11]	Hering, 2016 [12]
Minor AE, n (%) *(continuation)*	***Alternative immunosuppressive regimen:*** 9/36 (25%) switched to a nonsirolimus-based immunosuppressive regimen due to side effects: mycophenolate mofetil: 8, azathioprine: 1 ***Mild hepatic steatosis 2 years after transplantation:*** 4/13 subjects (31%), observed on routine MR imaging, were not associated with clinical sequelae). ***Renal function:*** Modest decline in creatinine clearance with a mild elevation in serum creatinine levels was observed over time (sometimes associated with increased albuminuria)	
Procedure-Related Complication rate	23/38 (61%) SAE were related to the study therapy, 18 of which were associated with hospitalization ***Procedure-related events:*** Acute intraperitoneal bleeding: 7/77 (9%), patients required subsequently: ■ Blood transfusion: 4 cases requiring blood ■ Laparotomy: 1 ■ Laparotomy after bile leak: 1 Severe hypoglycemia: 1 (had primary graft nonfunction immediately IT). Partial branch-vein occlusions: 2/36 (6%)	1 year FU: 22/30 SAEs[31] in 21 pts: Postprocedural bleeding: in 8.9% of transplants performed by percutaneous access of the portal vein but in none of the transplants performed by minilaparotomy. Only: Post procedural haemorrhage: 2 (2), Post procedural complication: 2 (2), Infusion site haemorrhage: 1 (1) were marked clearly as procedure-related bleeding events in the supplementary data
Survival rate, %	NR	100
Procedure-related mortality, n (%)	NR	0
Explantation	NR	NR
Islet graft feailure	10 subjects (28%) had complete graft loss (4 with primary nonfunction, 2 with early graft loss, and 4 who withdrew from further treatment)	NR
Length of stay, days	NR	NR

Abbreviations: AE … adverse event, C … control group, EORTC QLQ-C30 … European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 survey, FU … follow-up, I … intervention group, IEQ … islet equivalent, IQR … interquartile range, n … number of patients, NI … no information, NR … not reported, n.s. … not significant, P … p-value, SD … Standard deviation, pts … patients, QoL … Quality of life, SAEs … serious adverse events, s.s. … statistically significant, yrs … years

[31] No clear information which SAEs were procedure-related in the study

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [2] and in the Guidelines of EUnetHTA [3].

Table A-8: ROB2 of RCT endpoints comparing ICT versus insulin therapy, see [1]

Trial	Endpoints	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Lablanche 2018[4]	HbA1c	Low	High*	High†	Low	High§	High
	Fasting blood glucose	Low	High*	High†	Low	High§	High
	Hypoglycaemia	Low	High*	High†	Low	High§	High
	Insulin independence	Low	High*	High†	Low	High§	High
	Islet graft failure	Low	High*	High†	Low	High§	High
	Renal function	Low	High*	High†	Low	High§	High
	HRQoL	Low	High*	High†	Some concern‡	High§	High
	Complications	Low	High*	High†	Some concern‡	High§	High
	Adverse events	Low	High*	High†	Some concern‡	High§	High

Abbreviations: HRQOL … health-related quality of life, ICT … islet cell transplant, RCT … randomised controlled trial, T1D … type I diabetes

Notes:

* *Bias due to deviation from intended intervention assessed as high RoB due to open-label nature of study/lack of blinding; potentially resulting in 3 participants (ICT arm: 3.85% missing data; Insulin therapy arm: 8.33% missing data) withdrawing from the study prior to receiving allocated intervention, likely due to knowledge of the assigned intervention.*

† *Bias due to missing outcome data assessed as high RoB due to 3.85% missing data in ICT arm; 8.33% missing data in insulin therapy arm. No (sensitivity) analysis methods implemented to adjust for missing data and missingness could depend on participants health status.*

‡ *Bias in measurement of the outcome for HRQoL, complications and AEs assessed as high RoB due to subjective nature of these outcomes and lack of blinding/potential knowledge of intervention received may influence reporting.*

§ *Bias in selection of the reported result assessed as high RoB due to publication stating "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."*

Table A-9: ROBINS-I of NRSI comparing ICT alone versus pancreas transplant alone, see [3]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of interventione	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Maffi 2011[10]	Serious	Critical	Serious	Low	Low	Moderate	Serious	Critical	Nil

Abbreviations: ICT … islet cell transplant, NRSI … non-randomised studies of interventions, T1D … type I diabetes

Table A-10: ROBINS-I of NRSI comparing ICT with kidney transplant versus ICT alone, see [3]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of interventione	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Rickels 2022[5]	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Nil

Abbreviations: ICT … islet cell transplant, NRSI … non-randomised studies of interventions, T1D … type I diabetes

Table A-11: ROBINS-I of NRSI comparing ICT with insulin therapy, see [3]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of interventione	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Vantyghem 2009[8]	Moderate	Low	Low	Low	Serious	Serious	Moderate	Serious	Nil

Abbreviations: ICT … islet cell transplant, NRSI … non-randomised studies of interventions, T1D … type I diabetes

Table A-12: GRADE evidence profile (RCT): efficacy and safety of ICT compared to insulin therapy for T1D after kidney transplant

Quality assessment							Summary of findings				
Nº of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Other considerations	Number of patients		Effect		Quality
							ICT	Insulin	Relative (95% CI)*	Absolute (95% CI)	
HBA1C of less than 7% without severe hypoglycaemia (follow-up: 6 months)											
1	randomised trials	very serious[a]	not serious	very serious[b]	not serious	none	21/25 (84.0%)	0/22 (0.0%)	RR 0.16 (0.06 to 0.39)	NE[†]	⨁◯◯◯ Very low[a,b]
C-peptide – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
free from severe hypoglycaemia (follow-up: 6 months)											
1	randomised trials	very serious[a]	not serious	very serious[b]	not serious	none	17/25 (68.0%)	2/22 (9.1%)	RR 0.352 (0.196 to 0.633)	59 fewer per 1,000 (from 73 fewer to 33 fewer)	⨁◯◯◯ Very low[a,b]
β-score of 6 or higher (follow-up: 6 months)											
1	randomised trials	very serious[a]	not serious	very serious[b]	not serious	none	16/25 (64.0%)	0/22 (0.0%)	RR 0.360 (0.213 to 0.607)	NE[†]	⨁◯◯◯ Very low[a,b]
DQOL median gain in global score (follow-up: 6 months)											
1	randomised trials	very serious[a]	not serious	very serious[b]	not serious	none	25	22	-	median 16 point higher (NR)	⨁◯◯◯ Very low[a,b]
Mortality (follow-up: 6 months)											
1	randomised trials	very serious[a]	not serious	very serious[b]	not serious	none	0/25 (0.0%)	1/22 (4.5%)	NE[†]	NE[†]	⨁◯◯◯ Very low[a,b]
Procedural complications (follow-up: 6 months)											
1	randomised trials	very serious[a]	not serious	very serious[b]	serious[c]	none	5/25 (20.0%)	4/21 (19.0%)	RR 1.040 (0.313 to 3.467)	8 more per 1,000 (from 131 fewer to 470 more)	⨁◯◯◯ Very low[a,b,c]

Abbreviations: CI … confidence interval, HRQOL … health-related quality of life, ICT … islet cell transplant, NE … not estimable, NR … not reported, RCT … randomised controlled trial, RR … relative risk, T1D … type I diabetes

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Notes:

* *RR and corresponding 95% CIs imputed by assessment group using the following formulas: $RR = [a/(a + b)]/[c/(c + d)]$; lower bound $= exp[ln(RR) - Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$; upper bound $= exp[ln(RR) + Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$.*

† *Absolute/relative effects not estimable due to 0 events in one treatment arm*

[a] *High risk of bias*

[b] *Sample size between 1-99 patients therefore downgraded 2 levels[76]*

[c] *CI crosses the null*

Table A-13: GRADE evidence profile (NRSI): efficacy and safety of ICT compared to insulin therapy for T1D

Quality assessment							Summary of findings				
Nº of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Other considerations	Number of patients		Effect		Quality
							ICT	Insulin	Relative (95% CI)*	Absolute (95% CI)	
HBA1C (%) (follow-up: 3 years)											
1	Non-randomised studies	very serious[a]	not serious	very serious[b]	not serious	none	13	17	-	MD 1.5 percent lower (NR)	⨁◯◯◯ Very low[a,b]
C-peptide (follow-up: 3 years)											
1	Non-randomised studies	very serious[a]	not serious	very serious[b]	not serious	none	**I:** 11/13 patients had a blood C-peptide level <0.2 ng/mL **C:** NR				⨁◯◯◯ Very low[a,b]
Hypoglycemic events per week (follow-up: 3 years)											
1	Non-randomised studies	very serious[a]	not serious	very serious[b]	not serious	none	13	17	-	MD 1 event per week lower (NR)	⨁◯◯◯ Very low[a,b]
Graft failure – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
HRQOL – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mortality (follow-up: 3 years)											
1	Non-randomised studies	very serious[a]	not serious	very serious[b]	not serious	none	0/13 (0.0%)	0/17 (0.0%)	NE[†]	NE[†]	⨁◯◯◯ Very low[a,b]
Grade 3 or 4 adverse events (follow-up: 12 months)											
1	Non-randomised studies	very serious[a]	not serious	very serious[b]	not serious	none	**I:** 11/13 patients had a blood C-peptide level <0.2 ng/mL **C:** NR				⨁◯◯◯ Very low[a,b]

Abbreviations: C … comparator, CI … confidence interval, HRQOL … health-related quality of life, I … intervention, ICT … islet cell transplant, MD … mean difference, NE … not estimable, NR … not reported, NRSI … non-randomised studies of interventions, RR … relative risk, T1D … type I diabetes

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Notes:

⋆ *RR and corresponding 95% CIs imputed by assessment group using the following formulas:* $RR = [a/(a + b)]/[c/(c + d)]$;
$lower\ bound = exp[ln(RR) - Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$; $upper\ bound = exp[ln(RR) + Zc \times \sqrt{(1/a + 1/c - 1/(a + b) - 1/(c + d))}]$.

† *Absolute/relative effects not estimable due to 0 events in one treatment arm*

[a] *ROBINS-I assessed to be of serious risk of bias*

[b] *Sample size between 1-99 patients therefore downgraded 2 levels [76]*

Table A-14: GRADE evidence profile (NRSI): efficacy and safety of ICT compared to pancreas transplant for T1D

Quality assessment							Summary of findings				
Nº of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Other considerations	Number of patients		Effect		Quality
							ICT	Pancreas transplant	Relative (95% CI)*	Absolute (95% CI)	
HBA1C – not reported											
-	-	-	-	-	-	-	-				-
C-peptide – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Hypoglycemia – not reported											
-	-	-	-	-	-	-	-				-
Early graft failure (follow-up: 4 weeks)											
1	Non-randomised studies	extremely serious[a]	not serious	very serious[b]	not serious	none	5/33 (15.2%)	7/33 (21.2%)	RR 0.71 (0.25 to 2.02)	62 fewer per 1,000 (from 159 fewer to 216 more)	⨁◯◯◯ Very low[a,b]
HRQOL – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mortality (follow-up: 1 year)											
1	Non-randomised studies	extremely serious[a]	not serious	very serious[b]	not serious	none	0/33 (0.0%)	1/33 (3.0%)	NE[†]	NE[†]	⨁◯◯◯ Very low[a,b]
Adverse events (follow-up: 1 year)											
1	Non-randomised studies	extremely serious[a]	not serious	very serious[b]	not serious	none	**Pooled data: I vs C events:** CMV reactivation: 2 vs. 21 (p<0.001) Other infections: 2 vs. 5 ■ -Urinary tract infection: 0 vs. 3 ■ -Bacterial sepsis: 0 vs. 2 Necrotizing fasciitis: 0 vs. 1 Worsening kidney function: 5 vs. 4 ■ -End-stage RD: 1 vs. 2 ■ -Worsened DN: 1 vs. 3 ■ -Resolved after TW: 2 vs. 0 Other medical complications: ■ -Thrombotic TP: 0 vs. 1 ■ -Toxic hepatitis: 1 vs. 0 TAC-ind. Optic neuritis: 0 vs. 1				⨁◯◯◯ Very low[a,b]

Abbreviations: C … comparator, CI … confidence interval, CMV … Cytomegalovirus, DN … diabetic-nephropathy, HRQOL … health-related quality of life, I … intervention, ICT … islet cell transplant, NE … not estimable, NRSI … non-randomised studies of interventions, RD … renal disease, RR … relative risk, TAC … tacrolimus, T1D … type I diabetes, TP … thrombocytopenic purpura, TW … tacrolimus withdrawal,

GRADE Working Group grades of evidence: see Table A-13, page 113;

Notes: see also Table A-13, page 113 – except: [a] ROBINS-I assessed to be of critical risk of bias

Table A-15: GRADE evidence profile (NRSI): efficacy and safety of ICT alone compared to ICT with kidney transplant for T1D

Quality assessment							Summary of findings				
Nº of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Other considerations	Number of patients		Effect		Quality
							ICT alone	ICT with kidney transplant	Relative (95% CI)*	Absolute (95% CI)	
HBA1C of less than 7% without severe hypoglycaemia (follow up: median range 7.1 years to 8 years)											
1	Non-randomised studies	serious[a]	not serious	very serious[b]	not serious	none	24/48 (50.0%)	4/24 (16.7%)	RR 0.60 (0.43 to 0.84)	67 fewer per 1,000 (from 95 fewer to 27 fewer)	⨁◯◯◯ Very low[a,b]
C-peptide (follow up: median range 7.1 years to 8 years)											
1	Non-randomised studies	serious[a]	not serious	very serious[b]	not serious	none	**I:** Mean fasting C-peptide rose over the first 1 post-transplant year from undetectable levels to a peak of 1.7 ng/mL, fell to 1.3 ng/mL at 3 years, then more slowly to a mean of 1.2 ng/mL at the median follow-up of 5.6 years and 1.0 at 8 years. **C:** Mean fasting C-peptide rose over the first 1.2 post-transplant 4 years from undetectable levels to a peak of 2.0 ng/mL, and fell more rapidly to 1.5 ng/mL at the median follow-up of 3.3 years and 0.7 ng/mL at the end of follow-up at 7.1 years.				⨁◯◯◯ Very low[a,b]
Severe hypoglycemic events (follow up: median range 7.1 years to 8 years)											
1	Non-randomised studies	serious[a]	not serious	very serious[b]	serious[c]	none	3/48 (6.3%)	2/24 (8.3%)	RR 0.75 (0.13 to 4.19)	21 fewer per 1,000 (from 73 fewer to 266 more)	⨁◯◯◯ Very low[a,b,c]
Graft failure (follow-up: median range 39.3 months to 65.8 months)											
1	Non-randomised studies	serious[a]	not serious	very serious[b]	not serious	none	7/48 (14.6%)	9/24 (37.5%)	RR 0.41 (0.17 to 0.96)	221 fewer per 1,000 (from 311 fewer to 15 fewer)	⨁◯◯◯ Very low[a,b]
HRQOL – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mortality (follow up: median range 7.1 years to 8 years)											
1	Non-randomised studies	serious[a]	not serious	very serious[b]	not serious	none	0/48 (0.0%)	0/24 (0.0%)	NE[†]	NE[†]	⨁◯◯◯ Very low[a,b]
Adverse events (follow up: median range 7.1 years to 8 years)											
1	Non-randomised studies	serious[a]	not serious	very serious[b]	not serious	none	28/48 (58.3%)	15/24 (62.5%)	RR 0.93 (0.63 to 1.38)	44 fewer per 1,000 (from 231 fewer to 237 more)	⨁◯◯◯ Very low[a,b]

Abbreviations: C … comparator, CI … confidence interval, HRQOL … health-related quality of life, I … intervention, ICT … islet cell transplant, NE … not estimable, NRSI … non-randomised studies of interventions, RR … relative risk, T1D … type I diabetes

GRADE Working Group grades of evidence : see Table A-13, page 113;

Notes:

* *RR and corresponding 95% CIs imputed by assessment group using the following formulas: RR = [a/(a + b)]/[c/(c + d)]; lower bound = exp[ln(RR) – Zc × √(1/a + 1/c – 1/(a + b) – 1/(c + d))]; upper bound = exp[ln(RR) + Zc × √(1/a + 1/c – 1/(a + b) – 1/(c + d))].*

† *Absolute/relative effects not estimable due to 0 events in one treatment arm*

[a] *ROBINS-I assessed to be of moderate risk of bias*

[b] *Sample size between 1-99 patients therefore downgraded 2 levels [76]*

[c] *CI crosses the null and relatively wide*

Applicability table

Table A-16: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	***General population:*** Chronic pancreatitis: The estimated global point prevalence and incidence for CP is 74.77 and 34.81 per 100,000 population, respectively. Type 1 diabetes: As of 2021, the global point prevalence and incidence of T1D was 248.58 and 6.73 per 100,000 people, respectively. ***Austria population:*** Chronic pancreatitis: The prevalence and incidence in Austria is estimated at 192.55 and 59.04 per 100,000, respectively, in 2021. Type 1 diabetes: The prevalence and incidence of T1D is 615.04 and 11.12 per 100,000. Within this population, the prevalence and incidence of chronic kidney disease induced by complications of T1D is estimated at 173.91 and 2.25 per 100,000 people, respectively. ■ Limited information regarding the specific characteristics of the populations with chronic pancreatitis and type 1 diabetes has been identified. The participants in the studies for population 1 comprised a select group of adult patients with CP with presence of intractable pain and a diagnosis of CP. Given the stage of pancreatitis, this reflects the type of patients who would undergo pancreatectomy with autolougous islet cell transplantation in the Austrian health system. However, the results pertaining to these patient groups are not necessarily applicable to individuals who have additional comorbidities. The participants in the studies for population 2 (T1D with hypoglycemia and chronic renal failure) comprised a select group of adult patients with T1D in combination with hypoglycemia and the presence of chronic renal failure. Given the stage of renal failure and the presence of hypoglycemic events, this reflects the type of patients who would undergo kidney transplantation in combination with allogenic islet cells in the Austrian health system. However, the results are not necessarily applicable to individuals who have additional comorbidities. The participants in the studies for population 3 (diabetes type 1 with hypoglycemia and without kidney failure) comprised a select group of adult patients with hypoglycemaia. Given the stage of presence of hypoglycemic events, this reflects the type of patients who would undergo allogenic islet cell transplantation in the Austrian health system. However, the results are not necessarily applicable to individuals who have other comorbidities.
Intervention	Islet cell transplantation Utilisation, techniques, prerequisities and features of the technology are comparable between the intervention employed in the included studies and that used within the clinical setting in Austria
Comparators	Chronic pancreatitis: ■ No comparator Type 1 diabetes with kidney transplant: ■ Insulin therapy Type 1 diabetes: ■ Pancreas transplantation ■ Utilisation, techniques, prerequisities and features of the technology are comparable between the comparators in the included studies and that performed in Austria and Europe, broadly.
Outcomes	Outcomes Chronic pancreatitis: ■ Case series: Glycaemic control, insulin independence, exogenous insulin requirement, pain, analgesic use, quality of life, length of stay, mortality Type 1 diabetes with kidney transplant: ■ RCT included outcomes: Glycaemic control, insulin independence, islet cell graft failure, kidney function, quality of life, safety ■ NRSI with and without kidney transplant: Glycaemic control, insulin independence, exogenous insulin requirement, islet graft failure, kidney function, secondary diabetes complication, safety, survival rate ■ NRSI ICT vs insulin therapy: Glycaemic control, insulin independence, exogenous insulin requirement, islet graft failure, safety ■ Case series: Glycaemic control, insulin independence, exogenous insulin requirement, islet graft failure, kidney function, quality of life, safety, survival rate Type 1 diabetes: ■ NRSI ICT vs pancreas transplantation: Insulin independence, safety, islet graft failure, length of stay ■ Case series: Glycaemic control, insulin independence, exogenous insulin requirement, safety, survival rate, islet graft failure

Outcomes *(continuation)*	Follow up: Chronic pancreatitis: ■ Case series: 2-10 years Type 1 diabetes with kidney transplant: ■ RCT included outcomes: median 184 months ■ NRSI with and without kidney transplant: 2-3 years ■ NRSI ICT vs insulin therapy: 3 years ■ Case series: 3-10 years Type 1 diabetes: ■ NRSI ICT vs pancreas transplantation: 2-3 years ■ Case series: 1 year
Setting	Clinical settings ICT: ■ Islet cell transplantation is performed in a surgical environment setting, with islet transplantation occuring in a laboratory environment. Islets are transferred into the hepatic portal vein in a controlled operating room environment. All procedures are performed by a specialised and skilled surgeeon, with islet isolation being performed by specialised laboratory teams. This is common across Europe, Austria and the US and UK. [86] Geographical factors studies: Chronic pancreatitis: ■ Case series: US (2), UK (1) Type 1 diabetes with kidney transplant: ■ Randomised controlled trial: France (1) ■ Non-randomised studies of interventions: France (1), US (1) ■ Case series: France (2), US (1) Type 1 diabetes: ■ Non-randomised studies of interventions: UK (1), US (2)

Abbreviations: CP … chronic pancreatitis, ICT … islet cell transplant, NRSI … nonrandomised studies of interventions, RCT … randomised controlled trial, T1D … type 1 diabetes

List of ongoing randomised controlled trials

Table A-17: List of ongoing randomised controlled trials of ICT

Identifier/ Trial name	Study type	Condition	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date/Status	Sponsor
NCT02854696 STABILOT	Randomised, prospective, medico-economic nationwide French study	Patients with brittle type1 diabetes (T1D)	42	Islet graft	Best medical care (insulin treatment)	Incremental cost-utility ratio at 1 year	05/2023 Unknown status	University Hospital, Grenoble
NCT02803905 ITA-OMEN	Monocentric, Open-label, Double-arm, Phase II Trial	Patients with T1D	12	Arm A, n=6: Islet transplantation into the liver through the portal venous circulation	Arm B, n=6: ITA OMEN (islet directly into the omentum)	A1c </= 6.5% and no severe hypoglycemia after 1 year	12/2023 Active, not recruiting	Lorenzo Piemonti
NCT05095532	Randomised, controlled clinical trial	Chronic pancreatitis	42	One-time infusion of islets plus BM-MSCs at $20x10^6$/patient, n=14 **or** One-time infusion of islets plus BM-MSCs at $50x10^6$/patient, n=14	One-time infusion of islets only	Change in Islet Cell Function (1 year)	06/2026 Recruiting	Medical University of South Carolina
NCT03779139	Randomised pilot trial of patients	Chronic Pancreatitis	30	Intrahepatic islets alone	Experimental: Intrahepatic and omental pouch islets or Sham Comparator: Normal Volunteers	Portal vein thrombosis, Clavien-Dindo classification of surgical complications, Mixed Meal Tolerance Test, Intravenous Glucose tolerance test, Glucose potentiated arginine stimulation, Hypoglycemic clamp, Continuous glucose monitoring, Hemoglobin A1c levels, Insulin Use, Hypoglycemic episodes, Clarke score	12/2024 completed	University of Minnesota

Abbrevation: BM-MSCs … Bone Marrow Mesenchymal Stem Cell, n … number of patients, T1D … Type 1 Diabetes

Research questions

Table A-18: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

Table A-19: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-20: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?

Table A-21: Safety

Element ID	Research question
C0004	How does the frequency or severity of harms change over time or in different settings?
C0008	How safe is the technology in comparison to the comparator(s)?

Haute Authorite de Sante Health Technology Assesment

Based on a preliminary literature search, a report published by the French National Authority for Health, HAS (Haute Authorite de Sante) was identified. The HAS undertook a comprehensive health technology assessment on the topic of pancreatic islet transplantation, published in July 2020. The review investigated the safety and effectiveness of ICT across several populations:

- patients with chronically unstable insulin-deficient diabetes (T1D) with preserved renal function (allograft) (Population 3 of this current report);
- patients with insulin-deficient diabetes and renal failure (most often due to diabetic nephropathy) with an indication for renal transplantation, ICT being able to be simultaneous or deferred (allograft) (Population 2 of this current report);
- patients with insulin-deficient diabetes with a functioning kidney graft and presenting a HBA1c level ≥7% or severe hypoglycaemia (allograft);
- patients at risk of insulin-deficient diabetes following extensive or total pancreatic surgery or following pancreatic trauma resulting in extensive or total devascularization of the pancreas (autograft) (Population 1 of this current report).

These populations directly align with the populations of this current AIHTA report.

In line with best practice and using PICO tables developed for each population, HAS undertook a systematic search of literature in March 2020 with databases searched from inception. A number of databases were searched (Medline, the Cochrane Library, Science Direct, the National Guideline Clearinghouse, the International Network of Agencies for Health Technology Assessment [INAHTA] HTA Database). The searches also included grey literature searches of HTA agencies. All included studies were critically appraised using appropriate quality appraisal tools.

For Populations 2 and 3 (the use of ICT for T1D patients, with or without kidney transplant), the included evidence was INESSS (Institut national d'excellence en santé et services sociaux, Canada, report title: “Islet transplantation in people with unstable type 1 diabetes”), IHE (Institute of Health Economics, Canada, report title “Islet transplantation for the treatment of type 1 diabetes”), thirty-six original studies and a report from the Collaborative Islet Transplant Registry (CITR).

For population 1 (the use of ICT in patients at risk of insulin-deficient diabetes following extensive or total pancreatic surgery), three systematic review and meta-analyses were included.

Based on the literature review and stakeholder engagement, HAS recommended that ICT was a treatment option for all populations, based on certain conditions. A reassessment of this therapy is recommended in 5 years.

Due to the direct relevance of the HAS report to the current AIHTA review, the primary studies identified from the HAS report were independently assessed for inclusion, based on the AIHTA selection criteria. Separate comprehensive literature searches were undertaken to identify publications available since the search dates of the HAS report.

Literature search strategies

Search strategy for Cochrane

Search Name: Islet cell transplantation	
Search date: 20/12/2024 20:47:00	
Comment: MEL2024/25 (VH/AUS)	
ID	Search
#1	MeSH descriptor: [Pancreatitis] explode all trees
#2	(pancreatit*) (Word variations have been searched)
#3	MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#4	(T1DM)
#5	(T1D)
#6	(diabet*) (Word variations have been searched)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	MeSH descriptor: [Islets of Langerhans] explode all trees
#9	MeSH descriptor: [Islets of Langerhans Transplantation] explode all trees
#10	(islet* NEAR (cell* or langerhans* or transplant* or auto?transplant* or auto-transplant*)) (Word variations have been searched)
#11	#8 OR #9 OR #10
#12	#7 AND #10
#13	#7 AND #10 with Cochrane Library publication date Between Mar 2020 and Dec 2024
#14	#7 AND #10 with Publication Year from 2020 to 2024, in Trials
#15	#13 OR #14
#16	English:la
#17	German:la
#18	#16 OR #17
#19	#15 AND #18
#20	(conference proceeding):pt
#21	(abstract):so
#22	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#23	#20 OR #21 OR #22
#24	#19 NOT #23
#25	#19 NOT #23 in Trials
Total hits: 295	

Search strategy for Embase

Search Name: Islet cell transplantation		
Search date: 20.12.2024		
No.	Query Results	Results
#19.	#17 NOT #18	2,241
#18.	#17 AND 'Conference Abstract'/it	1,438
#17.	#16 AND [2020-2024]/py AND ([english]/lim OR [german]/lim)	3,679
#16.	#15 AND [2020-2024]/py	3,737
#15.	#13 OR #14	14,238
#14.	#11 AND #12	14,238
#13.	#11 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	1,254

#12.	'clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR longitudinal:ab,ti OR retrospective:ab,ti OR 'cross sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti	15,041,479
#11.	#5 AND #10	42,076
#10.	#6 OR #7 OR #8 OR #9	118,911
#9.	islet* NEAR/1 (cell* OR langerhans* OR transplant* OR auto$transplant* OR 'auto-transplant*')	55,440
#8.	'pancreas islet transplantation'/exp	10,080
#7.	'pancreas islet'/exp	88,173
#6.	'pancreas islet transplantation'/exp	10,080
#5.	#1 OR #2 OR #3 OR #4	672,979
#4.	diabet* NEAR/2 ('type 1' OR i OR 'insulin dependent')	522,670
#3.	'insulin dependent diabetes mellitus'/exp	169,911
#2.	pancreatit*	146,796
#1.	'chronic pancreatitis'/exp	26,560

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) ALL <1946 to December 19, 2024>	
Search date: 20.12.2024	
ID	Search
1	exp Pancreatitis/ (58472)
2	pancreatit*.mp. (81642)
3	exp Diabetes Mellitus, Type 1/ (90196)
4	T1DM.mp. (7406)
5	T1D.mp. (11980)
6	diabet*.mp. (914454)
7	1 or 2 or 3 or 4 or 5 or 6 (990131)
8	exp "Islets of Langerhans"/ (54214)
9	exp "Islets of Langerhans Transplantation"/ (9634)
10	(islet* adj3 (cell* or langerhans* or transplant* or auto?transplant* or auto-transplant*)).mp. (61183)
11	8 or 9 or 10 (73300)
12	7 and 11 (40544)
13	limit 12 to (clinical trial, all or observational study) (1182)
14	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (5391191)
15	12 and 14 (5653)
16	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (6974075)
17	((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (9222852)
18	16 or 17 (12090497)
19	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ (10161302)
20	hi.fs. or case report.mp. (764790)
21	19 or 20 (10827831)
22	18 not 21 (9495033)
23	12 and 22 (7573)
24	13 or 15 or 23 (10448)
25	limit 24 to yr="2020 - 2024" (1570)
26	limit 25 to (english or german) (1557)
27	remove duplicates from 26 (1554)

Search strategy for HTA-INATHTA

Search Name: Islet cell transplantation	
Search date: 20.12.2024	
ID	Search
6	(((islet*) AND (cell* OR langerhans* OR transplant* OR autotransplant* OR auto-transplant*)) OR ("Islets of Langerhans Transplantation"[mhe]) OR ("Islets of Langer-hans"[mhe])) FROM 2020 TO 2024,"0","2024-12-20T20:20:33.000000Z"
5	((islet*) AND (cell* OR langerhans* OR transplant* OR autotransplant* OR auto-transplant*)) OR ("Islets of Langerhans Transplantation"[mhe]) OR ("Islets of Langer-hans"[mhe]),"22","2024-12-20T20:20:22.000000Z"
4	((islet*) AND (cell* OR langerhans* OR transplant* OR autotransplant* OR auto-transplant*)) OR ("Islets of Langerhans Transplantation"[mhe]) OR ("Islets of Langer-hans"[mhe]),"22","2024-12-20T20:19:59.000000Z"
3	(islet*) AND (cell* OR langerhans* OR transplant* OR autotransplant* OR auto-transplant*),"20","2024-12-20T20:17:12.000000Z"
2	"Islets of Langerhans Transplantation"[mhe],"18","2024-12-20T20:15:46.000000Z"
1	"Islets of Langerhans"[mhe],"19","2024-12-20T20:15:19.000000Z"
Total hits: 0	

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