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► **To cite this version:**

Marie-Christine Vantyghem, Eelco J P de Koning, François Pattou, Michael R Rickels. Advances in β -cell replacement therapy for the treatment of type 1 diabetes. The Lancet, 2019, 394, pp.1274 - 1285. 10.1016/S0140-6736(19)31334-0 . hal-03488564

HAL Id: hal-03488564

<https://hal.science/hal-03488564>

Submitted on 20 Jul 2022

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1 **ADVANCES IN BETA CELL REPLACEMENT THERAPY FOR THE TREATMENT**
2 **OF TYPE 1 DIABETES**

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30 **Article type:** section, invited review

31 **Word count:** Main text: **4138** - Abstract: 150

32 **Material:** 3 figures 2 tables, no supplemental material

33 **Key words:** islet transplantation, stem cell therapy, type 1 diabetes, β -cell replacement
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35
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37
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39 **Abstract**

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41 The primary goal of treatment for type 1 diabetes is to control glycemia with insulin therapy in order to reduce
42 disease complications. For some patients, technological approaches to insulin delivery are inadequate, and
43 allogeneic islet transplantation is a safe alternative for those who have experienced severe hypoglycemia
44 complicated by hypoglycemia unawareness or glycemic lability, or who already receive immunosuppression for
45 a kidney transplant. Since 2000, intrahepatic islet transplantation has proven long-term efficacy in alleviating the
46 burden of labile diabetes and preventing long-term diabetes-related complications, whether or not a prior kidney
47 graft is present. Age, body mass index, renal and cardiopulmonary status help to choose between pancreas or
48 islet transplantation. Access is presently limited by the number of deceased donors and the necessity of
49 immunosuppression. Future approaches may include alternative sources of islets (xenogeneic tissue, human stem
50 cells), extra-hepatic sites of implantation (omental, subcutaneous, intramuscular), and immune tolerance or
51 encapsulation.

52

53 **Search strategy and selection criteria**

54

55 Data for this review were identified by searching MEDLINE, PubMed, Pubmed clinical trials, and references
56 from relevant articles using the search terms “islet transplantation”, “clinical” and “type 1 diabetes”, as well as
57 “ β -cell”, “stem cell”, “xenotransplantation”, “immune tolerance”. Articles published between 1990 and 2019
58 were included. We mostly selected publications from the past five years but did not exclude commonly
59 referenced and highly regarded older publications. We also searched the reference lists of articles identified by
60 this search and selected those we judged relevant. Review articles are cited to provide readers with more details.
61 Pancreas transplantation and islet auto-transplantation were excluded from this review.

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66 MAIN TEXT

67 The primary goal of treatment for type 1 diabetes (T1D) is to maintain blood glucose close to the normal range
68 in order to reduce disease-associated complications. Many patients can achieve this goal with intensive insulin
69 therapy, but at the price of frequent treatment-associated hypoglycaemia episodes.^{1,2,3,4} In contrast, β -cell
70 replacement therapy aims to maintain normoglycemia by restoring endogenous and regulated islet secretion of
71 insulin, and also of other islet hormones (Figure 1). The proof-of-concept of this more physiological approach
72 was provided 50 years ago by pancreas transplantation. In patients with T1D, the transplantation of a pancreas,
73 obtained from non-diabetic donors, can normalize blood glucose. Normoglycemia is then generally sustained as
74 long as alloimmune and autoimmune responses can be prevented by immunosuppression. Pancreas
75 transplantation has been associated with improvement in diabetic micro- and macroangiopathy, quality of life,
76 and likely, patient survival.⁵ However, pancreas transplantation carries a significant risk for surgical
77 complications, most of them related to the exocrine tissue. A less invasive alternative is islet transplantation (IT),
78 whereby the isolation of islets allows for ectopic transplantation of insulin and glucagon secreting cells, which
79 represent only a few milliliters of tissue volume. The efficacy of allogeneic intrahepatic IT to treat diabetes was
80 first shown in patients following pancreatectomy or with T1D.^{6,7} The promise of applying IT as an alternative for
81 treating T1D was confirmed in 2000, with the consistent achievement of one-year insulin-independence in seven
82 patients.⁸ Since then, more than one thousand T1D patients have been treated with IT alone or after kidney
83 transplantation for severe hypoglycaemia or poorly controlled glycaemia, as reported to the Collaborative Islet
84 Transplant Registry (CITR).⁹ This worldwide experience has confirmed the overall favourable safety profile of
85 IT.^{10,11,12} The improvement in metabolic outcomes has been confirmed in a randomized clinical trial *vs.*
86 optimized insulin therapy¹³ and now approach those of pancreas transplantation.¹⁴
87 The present review will focus on the current state-of-the-art of allogeneic IT, on its indications and limitations,
88 and finally on the various perspectives to overcome the presently limited numbers of islets and avoid life-long
89 immunosuppression.

91 What is islet transplantation?

92 Allogeneic IT aims at restoring appropriate insulin, glucagon, and other islet hormone secretion through the
93 engraftment of pancreatic islets of Langerhans in recipients with insulin-deficient diabetes, most often in patients
94 with T1D.

95 Currently, islets are isolated from a deceased donor pancreas, and then infused via the portal vein for delivery to
96 the liver under immunosuppression. The achievement of insulin-independence may require the infusion of two to
97 three islet preparations (goal at least 9,000 islets/kg recipient body weight), although a few centers have reported
98 high rates of insulin-independence with islets transplanted from a single donor pancreas provided at least 6,000
99 islets/kg were transplanted.^{15,16}

100 IT requires a close collaboration between national regulatory authorities, organ procurement organizations, tissue
101 typing laboratories, islet isolation facilities, transplant surgery, endocrinology, and interventional radiology
102 departments.

103

104 Islet isolation

105 Pancreatic islets are isolated from pancreases of deceased (brain-dead or non-heart beating) donors procured at
106 the time of anonymous multi-organ donation. In rare cases, islets have been isolated following partial
107 pancreatectomy from a living-related donor.¹⁷ Because of high surgical and metabolic risks, this technique is not
108 done routinely. Indeed over 40% of initially healthy living-related donors will develop glucose intolerance
109 following partial pancreatectomy, especially if they gain weight.¹⁸

110 Islets are isolated according to a standardized technique based on enzymatic and mechanical digestion followed
111 by density gradient purification.¹⁹ The resulting product is usually released for transplant if quantitatively the
112 number of islets obtained is more than 200,000, with favourable qualitative assessment of viability, purity, tissue
113 volume, and pathogens. However, the number of islets required may vary by center release criteria, patient size,
114 and/or whether it is a first or subsequent infusion.

115

116 Islet isolation is performed by a limited number of institutions worldwide (mainly in North America, Europe and
117 Australia). Taking into account the necessary 24-hour availability of islet isolation teams and complex
118 coordination, a low number of highly-specialized facilities seem more appropriate than several smaller units.
119 Indeed, pancreas procurement and transport should limit cold ischemia time, and islet facilities can ship islets to
120 regional centers for transplantation.

121 **Who will benefit from islet transplantation?**

122 Allogeneic ITA is an established therapeutic alternative for patients with T1D who have experienced severe
123 hypoglycemia complicated by impaired hypoglycemia awareness or excessive glycemic lability, as defined by
124 current practice recommendations and consensus reports (Figure 2).^{20,21} The main causes of hypoglycaemia and
125 glycemic lability (such as malabsorption, adrenal insufficiency, alcohol abuse...) should be ruled out, and
126 technological approaches should be attempted before IT (Figure 1).²⁰ Once a decision for transplantation has
127 been made, the choice between islet and pancreas transplantation should be discussed according to age, body
128 mass index, renal and cardiopulmonary status (Figure 2). ITA is usually proposed in cases of insulin-deficient
129 diabetes without clinically relevant kidney insufficiency, but complicated with glycemic lability and
130 hypoglycemia unawareness. The risk of immunosuppression is justified, by the four percent waiting-list
131 mortality rate of life-threatening hypoglycaemia.²²

132 When kidney insufficiency is present, combined pancreas-kidney transplantation remains the reference treatment
133 in the patients without cardiovascular morbidity. In patients with severe comorbidities, IT after (or
134 simultaneously to) kidney transplantation may be proposed even if diabetes is not unstable since the patient
135 already receives immunosuppression. IAK can be proposed in case of living or deceased donor kidney
136 transplantation, or after loss of a pancreas graft after combined pancreas-kidney transplantation or pancreas-after-
137 kidney transplantation. Pancreas transplantation alone or pancreas-after-kidney transplantation can also be
138 considered, in younger patients without cardiovascular morbidity.²³

140 **How does islet transplantation unfold?**

141 **Timetable and constraints for the patient**

142 As for all transplant interventions, IT first requires a pre-transplantation patient evaluation to assess the benefit-
143 risk ratio and ensure the patient is well-informed and provides consent. This is followed by transplant listing, the
144 eventual islet transplant, and repeated visits to ensure safety and efficacy monitoring.

145 The evaluation includes an assessment for hypoglycaemia unawareness and glycemic lability, diabetes-related
146 complications, the presence of kidney or liver disease, malignancies, and chronic infection. Losing excess body
147 weight, with a reduction of insulin requirement (in some studies, a cut-off value of < 60 units/day is used),
148 discontinuation of smoking, and lowering the level of glycosylated haemoglobin (HbA_{1c}) below 9%, are required
149 to ensure efficacy of the IT and minimize the risk for deterioration of retinopathic or neuropathic complications
150 upon the normalization of glycemic control post-transplant.

151 **Practical modalities of transplantation**

152 When an ABO compatible and cross-match negative islet preparation of sufficient quantity is available, a wait-
153 listed patient is called for image-guided surgical transmesenteric, or percutaneous transhepatic, islet infusion in
154 to the main portal circulation, with heparinization, and under general or local anaesthesia, respectively.^{8,24} Islets
155 might be transplanted freshly or after culture. Islet culture enables planning the transplantation within a 12-72-
156 hour time period, after the induction of immunosuppression. Islet culture may result in a modest decrease in islet
157 numbers, but likely enhances the quality and may reduce the immunogenicity of the preparation.

158 Patency of the main portal branch veins is assessed by monitoring of portal pressure during and Doppler
159 ultrasound after each infusion of islets. One to two days after the islet infusion, intravenous insulin instituted
160 during the transplant procedure is transitioned back to a subcutaneous route before tapering the insulin dosage
161 based on maintaining blood glucose values in the normal range. The immunosuppression regimen is adjusted
162 accordingly.

163 **Immunosuppressant treatment**

164 Immunosuppression includes an induction phase at each islet infusion, and then a maintenance phase during the
165 entire islet graft lifespan. Glucocorticoids are usually excluded.

166 The first clinically successful protocol for IT, the so-called Edmonton protocol, includes an anti-interleukin-2
167 receptor antibody (a T-cell activation inhibitor) before each islet infusion combined with sirolimus (an mTOR
168 inhibitor) and low-dose tacrolimus (a calcineurin-inhibitor).⁸

169 Variants of this protocol have been published since 2000, including 1) other induction agents such as T-cell
170 depleting agents (antilymphocyte globulin, alemtuzumab, or teplizumab) or lymphocyte tracking inhibitors such
171 as efalizumab;^{9,12,15,25-28} 2) other combinations of maintenance therapy (mycophenolate, everolimus, ciclosporin,
172 azathioprine, bela- or abatacept); 3) and the addition of steroids, or steroid-sparing anti-inflammatory agents that
173 inhibit TNF- α (etanercept, infliximab), or interleukin-1 β (anakinra, deoxyspergualine).^{9,15,29}

174 Currently, the Edmonton protocol is often replaced by an immunosuppressive regimen that includes
175 antithymocyte globulin with the first dose premedicated with one mg/kg methylprednisolone in order to mitigate
176 any side effects from cytokines released from the lysed T cells.¹¹ Subsequent islet infusions are then supported
177 with an anti-interleukin-2 receptor antibody, with all infusions including an etanercept course. Maintenance
178 therapy combines tacrolimus with either sirolimus or mycophenolate. There is currently no randomized trial to
179 assess the superiority of one protocol over the other.

180 **Transplantation monitoring**

181 The aim of monitoring is to detect rejection and the recurrence of autoimmunity using a minimal
182 immunosuppressive regimen, to screen for complications related to diabetes or immunosuppression, especially
183 opportunistic infections and neoplasia, and to assess the efficacy of the islet graft for restoring metabolic
184 balance. Consistent post-transplant monitoring is essential with weekly, then monthly visits in the first period
185 after transplantation, and regular visits or contacts thereafter. In contrast with a pancreas graft, islets are not
186 accessible for biopsy. Therefore, rejection is indicated mainly by deterioration in metabolic control that is
187 associated with a fall in C-peptide level. Treatment of acute rejection remains difficult even if steroids and
188 rituximab have been attempted.^{30,31} Rejection can be difficult to distinguish from recurrent autoimmunity
189 although monitoring of donor specific alloantibodies (DSA) and islet specific autoantibodies may be helpful.³²
190 T-cell auto and alloreactivity assays are not readily available in the clinic setting.³³

192 **What can be expected from islet transplantation?**

193 **Patient survival**

194 The five-year patient survival rate in CITR is close to 100%.^{9,10} It tends to be higher in islet transplantation
195 alone (ITA) as compared to islet-after-kidney (IAK) transplantation, but no significant difference has been
196 demonstrated until ten years although IAK patients generally have more severe preexisting diabetes-related
197 complications.¹⁴ In comparison, the mortality rate from hypoglycaemic events of wait-listed patients is almost
198 four percent.²²

199 **Insulin-independence**

200 Five-year insulin-independence rates may be as high as 60% (Table 1).^{9,14,34-38} A quarter of patients can remain
201 insulin-independent with HbA1c levels $\leq 6.5\%$, for at least ten years, with either ITA or IAK.¹⁴

202 **Metabolic control and hypoglycaemia**

203 Over years, the main goal of islet transplantation has evolved from achieving insulin independence to abrogation
204 of hypoglycaemia and restoration of impaired hypoglycaemia awareness. Even if insulin independence can be
205 reached, there is a progressive decline of graft function over time, which nevertheless allows long-term
206 satisfactory metabolic control.

207 In CITR, the 5-year persistence of graft function is around 60%-70% when T-cell depletion, TNF- α inhibition,
208 mTOR inhibitor, and /or sufficient islet mass are used and 40% in the rest of the IT population (Table 1).⁹ Ten-
209 year graft function can reach 75% in intention-to-treat, while maintaining a significant reduction of time spent in
210 hypoglycemia.^{14,35} Indeed, this decrease of severe hypoglycaemia and time spent in hypoglycaemia is the earliest
211 and most sustained benefit observed after IT, directly and inversely correlated to the C-peptide level, in parallel
212 to the restoration of counter-regulatory hormone responses, even if not complete.^{9,14,39-41} Several non-
213 randomized studies have also shown better metabolic results with IT compared with multiple daily injections of
214 insulin,^{42,43} subcutaneous or intraperitoneal insulin pumps without glucose sensors,^{24,35,44} and pancreas
215 transplantation (Table 2).⁴⁵⁻⁴⁷ A randomized study has confirmed these results at six months.¹³ A similar study
216 with a long-term follow-up and comparison to sensor-aumented insulin pump therapy is ongoing
217 (ClinicalTrials.gov identifier NCT03067324).

218 **Diabetes complications**

219 *Microangiopathy*

220 An important long-term outcome of clinical IT is the prevention or delay of diabetes-related complications. The
221 Diabetes Control and Complications Trial showed that a degree of sustained residual β -cell function in patients
222 with T1D on a basal-bolus insulin regimen was not only associated with fewer hypoglycemic episodes but also
223 with reduced risk of microvascular complications.¹ These observations led to the rationale that a certain degree
224 of endogenous insulin secretion, whether from eutopic or transplanted β -cells would have beneficial effects on
225 the occurrence or progression of diabetes-related complication, also in the presence of optimised insulin therapy.
226 With regard to the risk of nephropathy, the long-term beneficial effects of improved glycemia outweighs the
227 potential nephrotoxic effects of calcineurin inhibitors.¹⁴ In a study comparing patients on optimised insulin
228 therapy that were on the waiting list for an ITA with patients that had received ITA, the islet recipients
229 experienced less reduction of glomerular filtration rate over time.⁴⁸ In IAK, several studies have shown that there
230 was no change or even an improvement in kidney transplant function^{14,35} and no detriment to kidney function has
231 been observed long-term after loss of islet function.⁴⁹ Most of the adverse effects on kidney function appear to
232 be transient and related to the initiation of calcineurin inhibitors. Close monitoring is therefore necessary to
233 minimize the potential of adverse kidney events.

234 Compared with patients on optimised insulin therapy, patients after ITA have a reduced risk for progression of
235 retinopathy.^{36,37} Nevertheless, in patients with high HbA_{1c} levels before IT, rapid improvement in glycemic
236 control poses a risk for early vitreal haemorrhage after IT.

237 Several studies have shown stabilisation or improvement of diabetic peripheral sensory neuropathy.⁵⁰

238 *Macroangiopathy:* In cross-sectional studies comparing patients with T1D with a functioning kidney and islet
239 graft to patients with islet graft loss, or to kidney-only transplantation with optimised insulin therapy, the overall

240 survival and cardiovascular mortality rates were significantly better in patients with a functional IT over seven
241 years post-transplantation.⁵¹ ITA is associated with a stabilization of macroangiopathy in the CITR registry, or
242 even an improvement of different cardiovascular risk markers such as carotid intima-media thickness and
243 coronary calcifications as compared with pre-transplantation.^{9,52} A ten-year retrospective study has shown the
244 importance of systematic screening of silent ischemic cardiopathy, especially in over-5-year IAK patients.¹⁴

245 **Quality of life (QoL)**

246 IT is associated with long-term improvement in QoL, especially after ITA, largely due to the resolution of
247 hypoglycaemic events. Chronic diabetic complications, immunosuppression-related side effects and non-
248 achievement or loss of insulin-independence may attenuate this otherwise overall positive impact on QoL.⁵³ Of
249 note are reports of successful pregnancies after IT.⁵⁴

250 Therefore, in selected T1D patients, IT is associated with long-term improvement in metabolic control with less
251 hypoglycaemia and stabilized, improved or delayed chronic microvascular complications of diabetes than that
252 obtained with intensive insulin therapy.

253
254

255 **Risks**

256 The main risks of IT are related to the procedure, the immunosuppressive agents and exposure to additional HLA
257 antigens.^{55, 56}

258 The procedural risk of percutaneous transhepatic portal vein catheterisation followed by islet infusion includes
259 the occurrence of bleeding and portal vein thrombosis. While peritransplant heparin is used to reduce the risk of
260 thrombosis and increase islet survival, it increases the risk of hepatic bleeding. This risk is estimated to be less
261 than ten percent of procedures and includes perihepatic hematomas and intraabdominal or rarely intrapleural
262 hemorrhages, that may require blood transfusion or surgical interventions. The use of different types of
263 hemostatic plugs in the catheter tracts have reduced the bleeding risk over time.⁵⁷ Some centers perform
264 laparoscopic or minisurgical procedures using mesenterial veins to infuse the islets in the portal system.²¹ Portal
265 vein thrombosis is a rare complication in current practice, although branch vein clot occurs with an incidence
266 below five percent, possibly related to an increasing cumulative tissue volume. When portal branch vein
267 thrombosis is detected during routine follow-up soon after islet transplantation, longer-term anticoagulation is
268 indicated. Long-term ultrasound follow-up of IT patients can reveal patchy hepatic steatosis that is likely related
269 to locally high insulin concentrations.

270 One of the main barriers to IT is the requirement of immunosuppressive agents for the life of the graft. The main
271 risks of immunosuppression are uncommon, but include potentially severe infections and malignancies,
272 including *Epstein-Barr virus* (EBV)-induced lymphoproliferative disorders. The use of T-cell depleting agents
273 leading to more pronounced immunosuppression may increase this risk. Prophylaxis against *cytomegalovirus*
274 disease is commonly used, as is cotrimoxazole for the prevention of *pneumocystis*. Preventive measures against
275 malignancies include the avoidance of sun exposure and adherence to routine (especially skin) cancer screening.
276 Individual immunosuppressive drugs can each cause uncommon severe side effects.

277 The occurrence of DSA bears a theoretical risk of sensitization, and may be a barrier for future transplantation
278 Nevertheless, the risk of sensitization after multiple grafts does not appear to be greater than that of a single graft
279 (ten percent of cases), bearing in mind that alloreactivity with respect to successive mismatch seems to subside
280 with their repetition.⁵⁸ Also the maintenance of immunosuppression protects against sensitization and it seems
281 important to withdraw immunosuppression gradually in cases of islet graft failure unless it is still indicated to
282 support a functioning kidney graft.

283

284 **Prognostic Factors**

285 Prolonged insulin-independence after IT has now been demonstrated in numerous reports. However, like in
286 all other allogeneic transplantations, graft function often declines with time, resulting in the progressive
287 deterioration of glucose control and reintroduction of oral antidiabetic agents or small doses of insulin.
288 Numerous factors can, in theory, impact the outcomes of IT, including those related to the recipient baseline
289 characteristics, but also to the donors, the techniques used for preparing and administering the islets, as well
290 as to immunosuppression, rejection and recurrent auto-immunity.

291 In CITR,⁹ the five-year outcomes of IT appear similar when performed alone or after a kidney graft, and
292 better results are observed when the age of the recipient is above 35 years, with female gender, lower baseline
293 insulin requirement and HbA_{1c} level, and in the absence of pre-existing islet cell autoantibodies.

294 Among the graft characteristics, a higher number of transplanted islets, often in two or three separate
295 infusions, as well as a short period of islet culture prior to transplantation appear favourable.

296 Long-term IT outcomes appear also related to the type of immunosuppression administered, with regimens
297 combining induction therapy with T-cell depletion and/or TNF- α inhibitors and maintenance therapy with
298 mTOR inhibitor and/or calcineurin inhibitors being the most favourable. In recipients combining all these
299 favourable factors, the five-year rates of graft survival and insulin-independence were 69% and 47%,

300 respectively, and approaching the rates reported after solitary pancreas transplantation.²³
301 In T1D recipients, IT triggers immune reactions which are both innate and specific, autoimmune and
302 alloimmune, as well as humoral or cellular.⁵⁷ DSA are frequently detected in patients with poor graft survival,
303 and have been associated with HLA-DR mismatches and pre-existing panel reactive antibodies.⁵⁹ On the other
304 hand, de novo DSA in IT recipients may not directly impact graft survival.⁶⁰
305 Apart from their number, it seems obvious that qualitative characteristics of the transplanted islets also matter,
306 and various *in vitro*⁶¹ or *in vivo*⁶² assays have been proposed to estimate islet function. None of these tests is,
307 however, available at point of care, and their correlation with clinical outcomes remain to be established.
308 While islet purification is required to decrease the risk of portal vein thrombosis after IT, the persistence of
309 limited amounts of non-endocrine cells,³⁶ and/or presence of trapped islets⁹ are associated with better five-
310 year metabolic outcomes.
311 Finally, the initial graft function, which can be estimated with various biological proxies or by the initial
312 decrease of insulin requirement, appears highly predictive of later metabolic outcomes.⁹ Likewise, optimal
313 primary graft function, as documented by a near normal beta-score (a composite index based on C-peptide,
314 fasting glucose, HbA1c and insulin requirements) one month after the last islet infusion, is an excellent
315 predictor of long-term graft survival and insulin-independence.⁶³
316 Approximately less than ten percent of IT recipients experience procedure-related complications, which, even
317 when fully reversible, have a clear negative impact on later metabolic outcomes.^{9,64} Collectively, these results
318 suggest that, when allogeneic and autoimmune reactions can be efficiently prevented with
319 immunosuppression, the main determinant of long-term IT outcomes is the overall functional mass of islets
320 that initially survived the transplantation procedure.¹⁴
321

322 **Current limitations and future directions**

323 **Alternative islet sources**

324 While allogeneic IT is an established therapeutic alternative to insulin therapy, access is presently limited by the
325 availability of deceased donor pancreata for islet isolation and the accessibility of regional isolation facilities to
326 transplantation programs. The development of an islet source that makes on-demand, limitless manufacturing of
327 cell products possible, would significantly expand access to β -cell replacement therapy (Figure 3). Nevertheless,
328 it must still overcome significant safety concerns and inefficiencies in production. Porcine islets are the most
329 advanced xenogeneic source of islets for transplantation,⁶⁵ being available from established pathogen-free herds
330 and physiologically maintaining a similar blood glucose concentration as in humans. However, transplantation of
331 xenogeneic tissue presents a greater immunologic barrier than allogeneic tissue, with risk for hyperacute
332 rejection requiring more intensive immunosuppression. Also it introduces the potential for transmission of
333 zoonotic infections such as porcine endogenous retroviruses. Novel genome editing approaches are underway in
334 attempt to engineer porcine islets with lower immunogenicity and retroviral burden that promise to enhance
335 potential efficacy and safety of this cell source.⁶⁶

336 The differentiation of human stem cells to insulin-producing islets provides another potentially
337 unlimited cell source for IT.⁶⁷ Human embryonic stem (ES) cells can be differentiated *in vitro* to a pancreatic
338 endoderm progenitor stage, which following transplantation in mouse models, further differentiates *in vivo* into
339 insulin-producing islet tissue capable of reversing diabetes.^{68,69} However, off-target differentiation of pancreatic
340 ductal structures has been observed with longer-term follow-up of transplanted mice.⁷⁰ Therefore, the uncertain
341 potential for neoplastic transformation requires transplantation in sites where the cells can be readily monitored
342 and retrieved if necessary. Human ES cells can be further differentiated *in vitro* to a pancreatic islet cell stage
343 characterized by the capacity for glucose-dependent insulin secretion before transplantation that may also
344 reverse diabetes in mouse models.^{71,72} More research is required to determine whether further *in vitro*
345 differentiation can lower neoplastic potential and risk for developing non-islet tissue structures with ES cell
346 products, as well as to ensure the reproducibility and efficiency of this approach. Human ES cell-derived islets,
347 like deceased donor islets, are allogeneic and require immunoprotection. Stem cell-derived islets have also been
348 differentiated from patients with T1D using inducible pluripotent stem cells⁷³ and somatic cell nuclear transfer⁷⁴
349 that may abrogate alloimmunity. However, autoimmune recurrence is an obstacle faced by any human tissue
350 source.

351 **Alternative implantation sites**

352 The liver remains the most efficient site for islet engraftment as has been established for allogeneic IT, and is
353 successful in pre-clinical large animal models of porcine IT. For such mature islet cell products, access for
354 monitoring cellular identity is not necessary, but an alternative site capable of monitoring immune responses is
355 desirable. The only case of successful islet engraftment outside of the liver in a patient with T1D involved an
356 omental pocket created with a bioartificial thrombin scaffold,⁷⁵ which may be useful for patients with
357 contraindications to intraportal islet delivery. Nevertheless, the omental site is no more accessible for biopsy
358 monitoring or retrieval as may be required for stem cell-derived islets. Cases of intramuscular transplantation
359 using the brachioradialis muscle for the forearm have documented islet survival for autologous,⁷⁶ but not

360 allogeneic,⁷⁷ islets. The development of bioscaffolds capable of inhibiting islet cell death from hypoxia and
361 facilitating rapid re-vascularization for oxygen delivery will be necessary to support more efficient islet survival
362 in either an intramuscular or a subcutaneous site. Creation of a subcutaneous “device-less” space has been
363 successful in mouse models using deceased donor islets⁷⁸ and human ES cell-derived pancreatic endoderm cells
364 (PEC),⁷⁰ and requires further testing of diabetes reversal in large animal models.

365 **Alternative to immunosuppression**

366 The requirement for chronic immunosuppression has limited the current indication for IT to mainly those adult
367 patients who have experienced a severe hypoglycemia event complicated by hypoglycemia unawareness that
368 represent less than ten percent of the population with T1D.⁷⁹ The incorporation of antibodies blocking
369 costimulatory leukocyte functional antigen-1 (efalizumab) or CD28 on T lymphocytes (belatacept) has allowed
370 for the elimination of calcineurin-inhibitors that negates concern for immunosuppression-related
371 nephrotoxicity.⁸⁰ The long-term maintenance of insulin-independence with minimal, and, in one case no
372 maintenance immunosuppression, supports the possibility of one day achieving operational islet graft tolerance.
373 Until the induction of immunologic tolerance to allo- and autoantigens can be consistently established for
374 cellular therapy to treat T1D, immunoisolation of islet cell products is being pursued with encapsulation devices.
375 Recent results of human ES cell-derived PEC placed subcutaneously in a cell-impermeable device in patients
376 with T1D indicated PEC survival was significantly limited by a fibrotic foreign-body response.⁸¹
377 Immunoisolation via a macroencapsulation has to date only maintained human islet survival in a patient with
378 T1D when incorporating a refillable oxygen chamber within the device.⁸²

380 **Conclusion**

381 IT has proven its long-term efficacy over the last 20 years, both in alleviating the immediate burden of labile
382 diabetes and in preventing long-term diabetes-related complications, whether or not a prior kidney graft is
383 present. Allogeneic IT is currently a safe therapeutic alternative for patients with T1D who have experienced a
384 severe hypoglycemia event complicated by reduced hypoglycemia awareness or excessive glycemic lability.
385 Access is presently limited by the availability of deceased donor pancreata for islet isolation and the necessity of
386 immunosuppression. Future approaches may include alternative sources of islets, extra-hepatic sites of
387 implantation, and immunotolerance or immunoisolation, but these approaches still require more advanced phase
388 clinical testing.

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390 **Contribution of each author**

391 The four authors have equally contributed

392

393 **Declaration of interest**

394 The authors have no competing interest, regarding this manuscript.

395

396 **Acknowledgement**

397 No specific financial support was provided for the writing of this manuscript.

398 **Nevertheless** M.R.R. is supported in part by Public Health Services Research Grant R01 DK091331.

399 MCV and FP are or have been supported by the French Ministry of Health, PHRC (Programme hospitalier de
400 recherche clinique), the European Community (*Fond Européen de Développement Régional*), *Conseil Régional*
401 *du Nord-Pas-de-Calais* (IFR 114, *Institut de Médecine Prédictive et de Recherche Thérapeutique*), Programme
402 d'investissements d'avenir Labex European Genomic Institute for Diabetes ANR-10-LABX-46), the *Société*
403 *Française d'Endocrinologie*, the *Association de Recherche pour le Diabète*, *Santelys* and the *Agence de la*
404 *Biomédecine*.

405

406 **Figure Legends**

407 **Figure 1: Innovating treatments for type 1 diabetes**

408 The three innovating approaches for treatment of type 1 diabetes:

- 409 a. technological improvement of insulin delivery progressively evolving towards a closed loop system,
- 410 b. β -cell replacement therapy with islet transplantation being presented here, or with pancreas
- 411 transplantation,
- 412 c. preservation and regeneration or of residual native β -cells.

413 *italic: approaches which are still future directions*

414 **Figure 2: Indications for allogeneic islet β -cell replacement therapy in type 1 diabetes**

415 Pancreas transplantation alone or pancreas-after-kidney transplantation may be indicated in younger patients
416 without cardiovascular morbidity. A threshold for C-peptide $< 0.3\text{ng/mL}$ (100 pmol/L) is often considered but it
417 may vary according to kidney function and the technique of measurement. In some centers, insulin requirements
418 $< 60\text{ units/day}$ is used as cut-off point.

419 BMI: body mass index; eGFR: estimated glomerular filtration rate; LDK : living donor kidney transplantation
420 SPK: simultaneous pancreas-kidney transplantation; PAK: pancreas-after-kidney transplantation

421 **Figure 3: Current and future approaches to β -cell replacement therapy in type 1 diabetes (T1D)**

422 Green, the current clinical approach uses allogeneic islets isolated from a deceased donor as the β -cell source,
423 delivery via portal vein infusion for intrahepatic engraftment, and standard T lymphocyte directed induction and
424 maintenance immunosuppression.

425 Orange, a case of successful transplantation of allogeneic islets into an omental pouch created with a thrombin
426 bio-scaffold has been reported,⁷⁵ and a case of successful intrahepatic transplantation of allogeneic islets has
427 documental operational islet graft tolerance following withdrawal of maintenance immunosuppression provide
428 proof-of-concept for the possibility of extra-hepatic and immunosuppression-free islet transplantation in humans.

429 Purple, pre-clinical approaches without as of yet document success in reversing diabetes in human T1D.

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Table 1: Overview summary of one and five-year metabolic outcomes after islet transplantation since 2004

Twenty-two studies were included in this updated review when graft function, insulin independence or the composite criteria of good metabolic balance with HbA1c < 7% (53 mmol/mol) associated with suppression of severe hypoglycemia events (SHEs), with at least 1-year and up to 5-year follow-up were clearly reported. Outcomes are described by median, IQR, Min, and Max rates. The number of studies and patients is mentioned in the analysis.

- Fifteen studies reported data from ITA recipients alone: Hering BJ. et al. (PMID 14961992); Hering BJ. et al.¹⁵; Ryan E. et al. (PMID 15983207) (including a subgroup analysis on patients who completed the islet transplant procedure); Froud T. et al. (PMID 15996257) (including a subgroup analysis on patients who completed the islet transplant procedure; five out of fourteen patients were retransplanted); Shapiro AMJ. et al.⁵⁶ (In this study, insulin independence was associated with HbA1c < 6.5%); Huurman V. et al. (PMID 18560516); Bellin MD. et al. (PMID 18808408); Turgeon NA. et al.²⁵; Matsumoto S. et al. (PMID 21396171) (one out of three patients from the group Anakinra was retransplanted); Maffi P. et al.⁴⁵ (18/33 pre-transplant treatment with sirolimus, this study included a subgroup analysis of patients who achieved insulin independence (19/33) with Kaplan-Meier estimates); O'Connell PJ. et al.¹²; Rickels MR. et al.¹⁶; Qi M. et al.³⁴ (three out of six patients from the group etanercept/exenatide were retransplanted); Maffi P. et al. (PMID 25286053); Hering BJ. et al. (PMID 27208344).

- Three studies reported data from IAK or SIK recipients alone: Cure P. et al. (PMID 18360260); Tan J. et al. (PMID 18633105); Lehmann R. et al.³⁵

- And finally, four studies reported data from both ITA and IAK recipients: Deng S. et al. (PMID 19920782) (including a subgroup analysis on patients who completed the islet transplant procedure); Lablanche S. et al.³; Lablanche S. et al.¹³; Vantighem MC. et al.¹⁴

- All trials were phase 1/2, interventional, non-randomized, single arm, open label studies, excepted: Froud T. et al. (PMID 15996257) (Phase 2, randomized, parallel assignment, open label); Hering BJ. et al. (PMID 27208344) (Phase 3, non-randomized; single arm; open label) and Lablanche S. et al.¹³ (Phase 3, randomized; parallel assignment; open label)

- abbreviations : IQR: Inter Quartile Range Q1-Q3; ITA: Islet Transplantation Alone; IAK: Islet After Kidney; Min: minimum; Max: maximum; SIK: Simultaneous Islet-Kidney Transplantation; SHEs: Serious hypoglycemic events.

PMID is given when references were not quoted in the main text.

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Table 2: Comparison of islet transplantation to other reference treatments

All comparisons are given as IT compared to the control group:

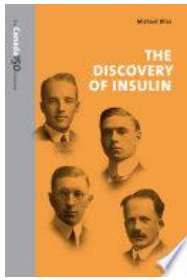
➔: similar; ↗: higher; ↘: lower (in islet transplantation as compared to the control group)

All studies are single center except otherwise indicated

Insulin-free rates are given at the end of the follow-up period either otherwise indicated

*the study did not aim at gaining insulin-independence

ATG: thymoglobulin; CMV: cytomegalovirus; CGM: Continuous glucose monitoring; CSII: Continuous subcutaneous insulin infusion; DIN: Daily Insulin Need; eGFR: estimated Glomerular Filtration Rate; Hypo: Hypoglycemia; IAK: Islet after kidney transplantation; IT: islet transplantation; ITA: Islet Transplantation Alone; KTA: kidney transplantation alone; MDI: multiple daily injection; MG: Mean glucose on CGM; MMF: mycophenolate; PAK: Pancreas after kidney transplantation; PTA: pancreas transplantation alone; SD: standard deviation of mean glucose on CGM; sir: sirolimus; SIK: Simultaneous islet–kidney transplantation; SHEs: Severe hypoglycaemia events; SPK: Simultaneous kidney-pancreas transplantation. T1D: type 1 diabetes; tac: tacrolimus; yr: year.



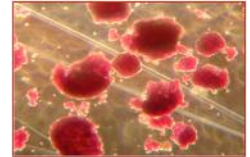
The discovery of insulin



Multiple daily insulin injections (MDI)
Sensor-augmented MDI

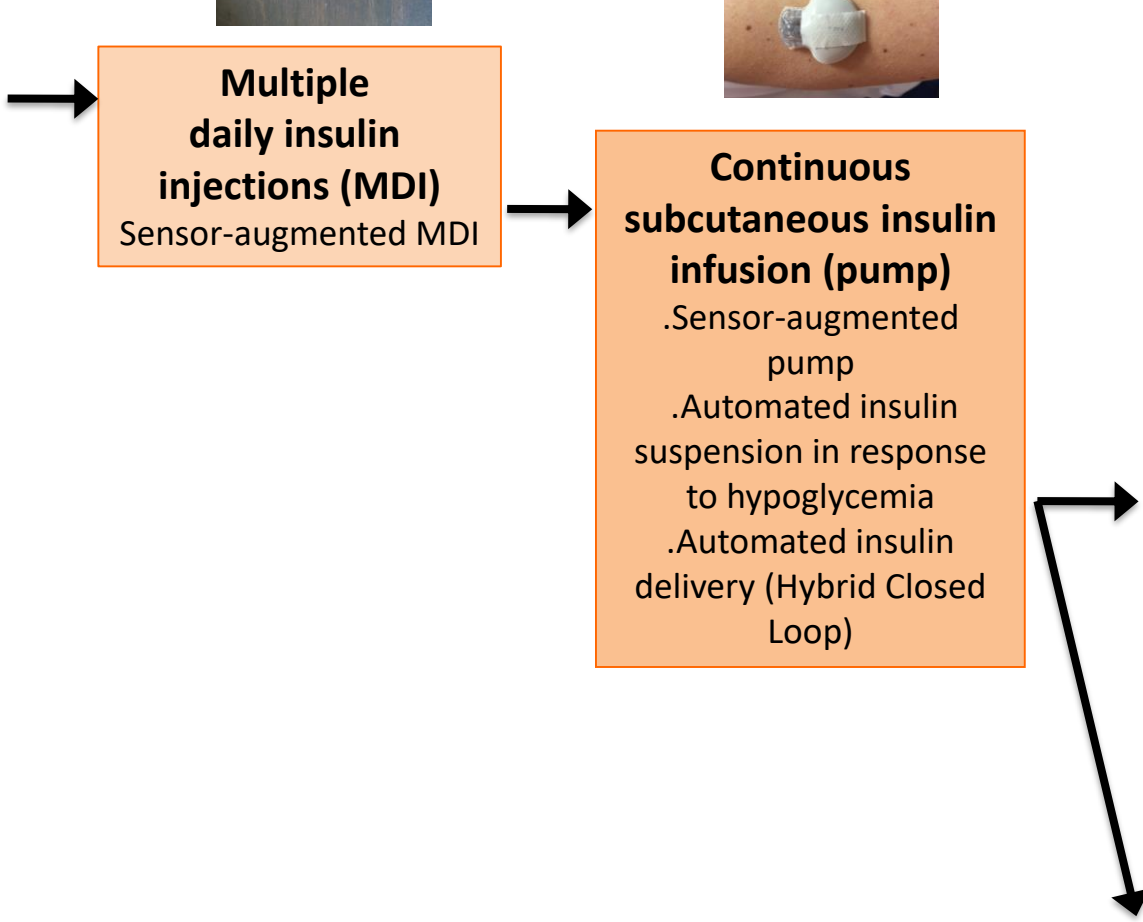


Continuous subcutaneous insulin infusion (pump)
.Sensor-augmented pump
.Automated insulin suspension in response to hypoglycemia
.Automated insulin delivery (Hybrid Closed Loop)



β cell replacement (transplantation)
Whole pancreas
Isolated islets
Stem cell-derived islets
Xenogeneic islets

β cell regeneration
Replication,
Neogenesis,
Transdifferentiation



T1D receiving intensive insulin therapy

Negative or very low C-peptide
No substance abuse or tobacco use
HbA1c < 9 % - BMI < 28-30 kg/m²
Treated diabetes-related complications
No malignancies

Preserved kidney function

Age ≥ 25-35 years
Insulin requirement < 1 unit/kg/day
Labile diabetes or hypo unawareness
≥ 1 SHE/year

Islet transplantation alone

Presence of a kidney graft

Stable eGFR, proteinuria < 0.3 g/day
Insulin requirement < 1 unit/kg/day

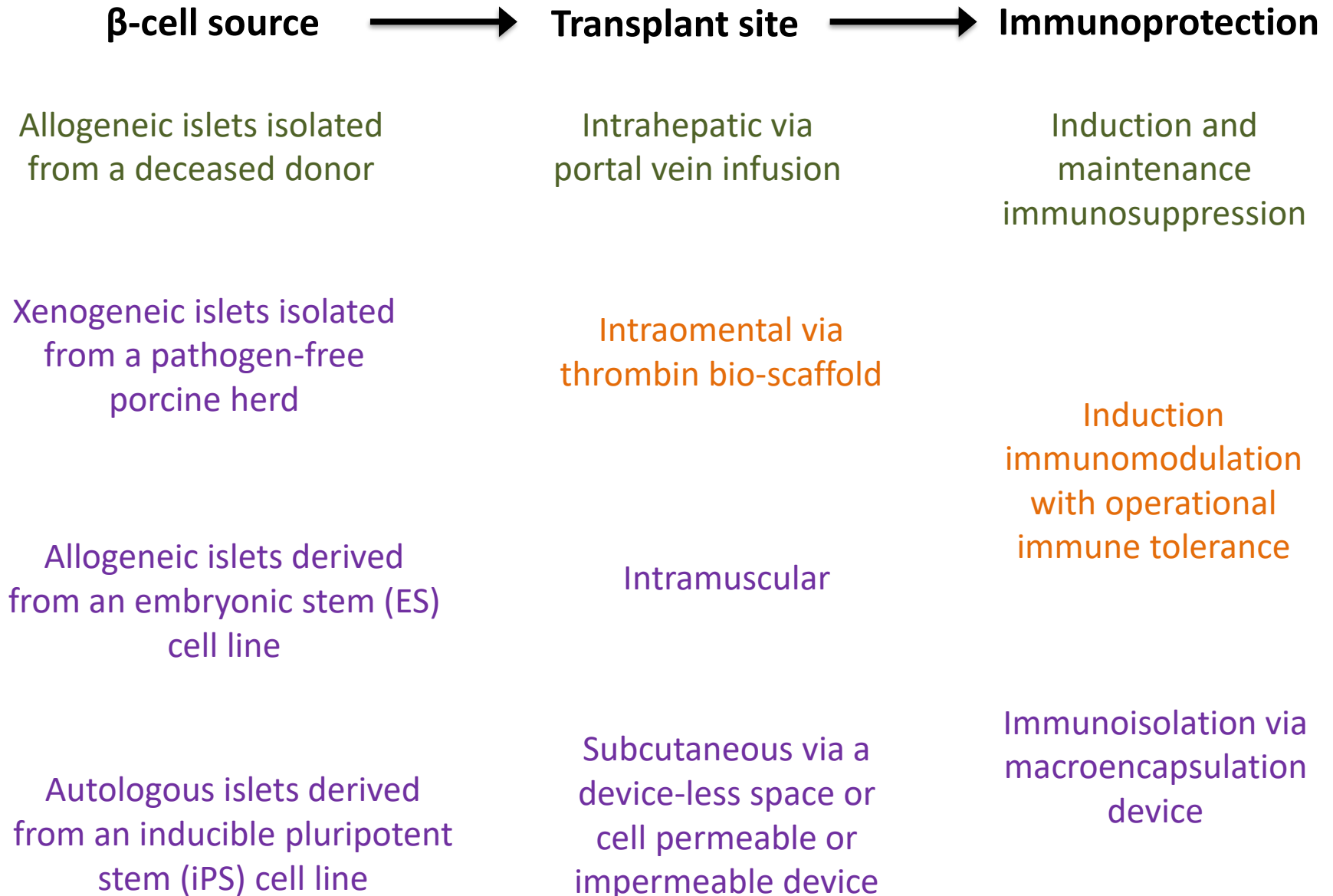
Islet after kidney

possible after deceased donor
or LDK transplantation
or after loss of a pancreas
transplant after SPK or PAK

ESRD

eGFR < 30 mL/mn
SPK not desired or indicated
age > 45-55 years
severe macroangiopathy

**Islet simultaneous to kidney
transplantation** possibly pre-
emptive to starting dialysis
or
kidney transplantation alone



Graft Function
% of patients

	1 year			5 years		
	Median (IQR)	Min-Max	N. of studies/patients	Median (IQR)	Min-Max	N. of studies/patients
ITA recipients	93 (75-100)	50 to 100	22/254	81 (78-100)	74 to 100	6/34
IAK/SIK recipients	93 (88-100)	86 to 100	5/52	80 (74-85)	74 to 85	2/24

Insulin Independence
% of patients

	1 year			5 years		
	Median (IQR)	Min-Max	N. of studies/patients	Median (IQR)	Min-Max	N. of studies/patients
ITA recipients	67 (50-82)	38 to 100	23/170	40 (14-50)	8 to 100	7/20
IAK/SIK recipients	51 (28-74)	20 to 83	6/21	32 (9-54)	9 to 54	3/7

HbA1c < 7% (53mmol/mol) and no SHEs
% of patients

	1 year			5 years		
	Median (IQR)	Min-Max	N. of studies/patients	Median (IQR)	Min-Max	N. of studies/patients
ITA recipients	82 (69-94)	40 to 100	9/121	54 (50-90)	50 to 100	4/13
IAK/SIAK recipients	86 (80-86)	80 to 86	3/18	59 (58-60)	58 to 60	3/7

Islet transplantation	Study design	ITA IAK	T1D control	IT Immuno suppression	Follow-up yr	Insulin free %	HbA1c	SHEs	Adverse events
vs. Optimized insulin therapy									
Vantyghem 2009 ²⁴	Non-randomized retrospective	7 ITA 6 IAK	17 intra peritoneal pump	Edmonton	3	46 %	↘ 6.6 vs 8.1%	↘	↗
Thompson 2011 ⁴²	Prospective cross-over cohort	32 ITA	45	ATG+tac+ MMF	> 5	37%	↘ 6.7 vs 7.8%	-	-
Gerber 2015 ⁴³	Non-randomized retrospective	22 IAK or SIK	#1: 70 MDI or CSII #2:13 KTA	Edmonton	7	5-yr: 9 %*	↘ 6.7 vs 8.2 preIT 7.6 % (#1) 7.9 % (#2)	↘	↗
Lablanche 2018 ¹⁴	Multicentre, open-label, randomized controlled	25 ITA or IAK	21:CSII or MDI	ATG+steroid bolus + tac + MMF + etanercept	1	59 %	↘ 5.8 vs 8.1%	↘ 0 vs 2%	↘ one death related to SHEs on waiting list
vs. Pancreas transplantation									
Franck 2004 ⁴⁷	Non-randomized retrospective	9 ITA 4 IAK	25 SPK 5 PAK	Edmonton	3	↘	↗	→ 0 vs 0%	↘
Maffi 2011 ⁴⁵	Non-randomized retrospective	33 ITA	33 PTA	Edmonton or ATG+MMF+sir± pre-IT	1	↘ 59 vs 75%	-	-	↘
Lehman 2015 ³⁵	Non-randomized retrospective	38 SIK or IAK	94 SPK or PAK	Edmonton then sir switched to MMF, daclizumab switched to basiliximab/ ATG	> 5	↘ 9 vs 73%*	↗ 6.5 vs 5.9%	→ drop by 90% vs pre-IT	↘ 10 vs 41%