Indications for islet or pancreatic transplantation: Statement of the TREPID working group on behalf of the Société francophone du diabète (SFD), Société francaise d'endocrinologie (SFE), Société francophone de transplantation (SFT) and Société française de néphrologie – dialyse – transplantation (SFNDT)

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Anne Wojtusciszyn[1] *, Julien Branchereau[2]*, Laure Esposito[3], Lionel Badet[4], Fanny Buron[5], Mikael Chetboun[6], Laurence Kessler[7], Emmanuel Morelon[8], Thierry Berney[9], François Pattou[6], Pierre-Yves Benhamou[8]*, Marie-Christine Vantyghem[10]* and the TREPID group

* These authors contributed equally to this report

[1] Email: a-wojtusciszyn.@chu-montpellier.fr

Department of Endocrinology, Diabetes and Nutrition, University Hospital of Montpellier, Lapeyronie Hospital; Laboratory of Cell Therapy for Diabetes (LTCD), Institute of Regenerative Medicine and Biotherapy, (IRMB), University Hospital of Montpellier, Saint Eloi Hospital; and IGF, CNRS UMR5203, INSERM U1191, Montpellier University, F-34094 Montpellier, France

[2] Email: julien.branchereau@chu-nantes.fr

Urology Department, CHU Nantes; Centre de Recherche en Transplantation et Immunologie, UMR 1064, INSERM, Université de Nantes; and Institut de Transplantation Urologie Néphrologie (ITUN), CHU Nantes, Nantes, France

[3] Email: esposito.l@chu-toulouse.fr

Department of Nephrology CHU Toulouse, Toulouse, France; and INSERM, U1055, F-38000 Grenoble, France

[4] Email: lionel.badet@chu-lyon.fr

Hospices Civils de Lyon, Service d'Urologie et de Chirurgie de la Transplantation, Pôle Chirurgie, Lyon, France

[5] Email: fanny.buron@chu-lyon.fr

Hospices Civils de Lyon, Service d'Urologie et de Chirurgie de la Transplantation, Pôle Chirurgie, Lyon, France

[6] Email: mikael.chetboun@univ-lille2.fr

University of Lille, INSERM, CHU Lille, UMR 1190; Translational research in diabetes; CHU Lille, Endocrine Surgery, F-59000, Lille, France

[6] Email: Laurence.Kessler@chru-strasbourg.fr

Department of Endocrinology and Diabetology, University Hospital of Strasbourg, France; INSERM UMR 1260, Regenerative Nanomedicine, Federation of Translational Medicine, University of Strasbourg, F-67000 France

[7] Email: emmanuel.morelon@chu-lyon.fr

Hospices Civils de Lyon, Service d'Urologie et de Chirurgie de la Transplantation, Pôle Chirurgie, Lyon, France

[8] Email: Thierry.Berney@hcuge.ch

Division of Transplantation, Department of Surgery, University of Geneva Hospitals, Geneva, Switzerland

[6] Email: fpattou@univ-lille2.fr

University of Lille, INSERM, CHU Lille, UMR 1190, Translational research in diabetes; CHU Lille, Endocrine Surgery, F-59000, Lille, France

[9] Email: PYBenhamou@chu-grenoble.fr

Department of Endocrinology, Pôle DigiDune, Grenoble University Hospital, Grenoble Alpes University, LBFA; INSERM, U1055, F-38000 Grenoble, France

[10] Email: mc-vantyghem@chru-lille.fr

University of Lille, INSERM, CHU Lille, UMR 1190, Translational research in diabetes; CHU Lille, Endocrinology, diabetology and metabolism, F-59000, Lille, France

TREPID group members:

Andres Axel, Armanet Mathieu, Blancho Gilles, Caillard Sophie, Catargi Bogdan, Cattan Pierre, Chailloux Lucy, Choukroun Gabriel, Ciacio Oriana, Cuellar Emmanuel, Donatini Gianluca, Duffas

Jean-Pierre, Durrbach Antoine, Elias Michelle, Frimat Marie, Garrigue Valérie, Gaudez Francois, Hanaire Hélène, Kamar Nassim, Karam Georges, Lablanche Sandrine, Lejay Anne, Le Mapihan Kristell, Malvezzi Paolo, Melki Vincent, Moreau Karine, Muscari Fabrice, Ohlmann Sophie, Panaro Fabrizio, Peraldi Marie-Noelle, Pittau Gabriella, Prévost Gaetan, Reffet Sophie, Riveline Jean-Pierre, Sacunha Antonio, Serre Jean-Emmanuel, Tetaz Rachel, Thaunat Olivier, Tillou Xavier, Vidal-Trecan Tiphaine

Corresponding author:

Marie-Christine Vantyghem

Service d'Endocrinologie et Métabolisme, Hôpital C Huriez Centre Hospitalo-universitaire de Lille, 1 rue Polonovski, 59 037 Lille Cedex France

Tel: +3332 0444 535, Fax: +3332 0446 985

Email: mc-vantyghem@chru-lille.fr

Abbreviations: ABM: French biomedicine agency; BMI: body mass index; CGM: continuous glucose monitoring; CITR: Collaborative International Transplantation Registry; CV: coefficient of variation; GAD: glutamic acid decarboxylase; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; IAK: islet after kidney transplantation; IIP: implantable insulin pump; IS: immunosuppression; IT: islet transplantation; ITA: islet transplantation alone; MODY: maturity-onset diabetes of the young; MRI: magnetic resonance imaging; OGTT: oral glucose tolerance test; PAK: pancreas after kidney transplantation; PTA: pancreas transplantation alone; QoL: quality of life; SD: standard deviation; SIK: simultaneous islet–kidney transplantation; SPK: simultaneous pancreas–kidney transplantation; T1D: type 1 diabetes

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ABSTRACT

While either pancreas or pancreatic islet transplantation can restore endogenous insulin secretion in patients with diabetes, no beta-cell replacement strategies are recommended in the literature. For this reason, the aim of this national expert panel statement is to provide information on the different kinds of beta-cell replacement, their benefit–risk ratios and indications for each type of transplantation, according to type of diabetes, its control and association with end-stage renal disease. Allotransplantation requires immunosuppression, a risk that should be weighed against the risks of poor glycaemic control, diabetic lability and severe hypoglycaemia, especially in cases of unawareness. Pancreas transplantation is associated with improvement in diabetic micro- and macroangiopathy, but has the associated morbidity of major surgery. Islet transplantation is a minimally invasive radiological or mini-surgical procedure involving infusion of purified islets *via* the hepatic portal vein, but needs to be repeated two or three times to achieve insulin independence and long-term functionality. Simultaneous pancreas–kidney and pancreas after kidney transplantations should be proposed for kidney recipients with type 1 diabetes with no surgical, especially cardiovascular, contraindications. In cases of high surgical risk, islet after or simultaneously with kidney transplantation may be proposed. Pancreas, or more often islet, transplantation alone is appropriate for non-uraemic patients with labile diabetes. Various factors influencing the therapeutic strategy are also detailed in this report.

Keywords: Cell therapy; Diabetes; Islet transplantation; Kidney transplantation; Pancreas transplantation; Type 1 diabetes

INTRODUCTION

Either pancreas or pancreatic islet transplantation can restore endogenous insulin secretion in patients with diabetes. Pancreatic transplantation has been performed since 1966, with protocols and surgical procedures that have continually improved over time. Over 45,000 pancreatic transplantations have been performed, and the effectiveness of the technique in restoring beta-cell function is well established. Pancreas transplantations have also been associated with improvement in diabetic micro- and macroangiopathy, although the risk of morbidity is similar to that of major surgery. Pancreatic islet transplantation is a minimally invasive radiological or mini-surgical procedure involving infusion of purified islets *via* the hepatic portal vein. Since 2000, with the achievement of insulin independence after 1 year in all patients treated by this graft procedure in Edmonton, Alberta, Canada [1], islet transplantation results have also continuously improved and now tend to have metabolic results comparable to those of pancreas transplantation for at least up to 3 years post-transplantation [2]. However, two or more donor organs are usually required for successful islet transplantation.

Both techniques may be proposed as therapeutic options in selected recipients. As patients need long-term immunosuppression (IS) to preserve graft function, these transplants increase the risk of IS-related adverse events, and each technique has complications due to its specific transplant procedures. These risks have to be weighed against poor glycaemic control, diabetes lability and severe hypoglycaemia, especially in cases of unawareness. The correct indications and benefit–risk ratios therefore depend on different factors, all of which are presented here, when choosing the best transplantation option for each given patient.

However, the small number of donor pancreases limits the availability of these treatments and the experience of each centre, thereby making it difficult to conduct prospective randomized controlled trials on the overall efficacy and safety of these therapies compared with each other or with exogenous insulin treatment. Nevertheless, the recently published TRIMECO trial has shed some light by comparing islet transplantation with standard care using exogenous insulin [3]. Thus, recommendations are now urgently needed on the respective indications for these procedures, as 10-year results are now available for both techniques [4, 5].

To our knowledge, there are no recent detailed international recommendations for either pancreas or islet transplantation in a given patient, despite the availability of recommendations for islet transplants in some countries. The UK National Institute for Health and Care Excellence (NICE; nice.org.uk/guidance/ipg257), for example, issued procedural guidance for allogeneic islet transplantation in 2008, whereas based on the experience gained since the world-renowned 'Edmonton protocol' was first used [1], the Canadian Diabetes Association Clinical Practice Guidelines Expert Committee published a statement in 2013 with a brief description of the results and risks with both techniques [6]. The American Diabetes Association (ADA) outlined indications for pancreas transplantation in 2006, but only mentioned islet transplantation as a technique in need of more controlled studies. In 2014, however, the ADA provided more information on indications for pancreas transplantation alone (PTA) or pancreas after kidney transplantation, including that simultaneous pancreas–kidney and pancreas after kidney transplantations should be proposed to kidney recipients with type 1 diabetes (T1D) and that PTA is appropriate for non-uraemic patients with labile diabetes [7]. This statement, however, remains vague on islet transplantation indications.

Nevertheless, evidence-based recommendations defining the respective roles of islet and pancreas transplantation in cases of severe hypoglycaemia have been published by an international panel [8]. Islet transplantation has specific indications and is a recognized routine procedure for selected patients in several countries, including Canada, the UK, Belgium and Switzerland. In France, islet grafts are still performed only in clinical trials, but the situation is changing rapidly, and French groups have had good results in this area since the end of the 1990s. Yet, despite vast experience with islet [3, 4, 9] and pancreas [10–12] transplantation, recommendations are still not available. Thus, the goal of the present statement is to provide the necessary information to remedy this lack.

According to the French Biomedicine Agency (ABM; www.agence-biomedecine.fr*)*, > 2000 pancreas transplantations have been performed in France since the first such operation in 1976, with 90% of them being simultaneous pancreas–kidney (SPK) transplants. While > 200 patients were on the waiting list in 2017, only 70–100 pancreas transplantations are performed each year. The 10-year pancreas graft survival for SPK transplantations performed during 2005–2008 is about 60%. As for islet grafts, 25–50 islet injections are performed each year in France and, since the 1990s, > 100

patients have received islet transplants, with 80% of cases having indications for islets alone. The number of islet-transplanted patients worldwide, according to the Collaborative International Transplantation Registry (CITR; www.citregistry.org), is > 1000, with a mean of two islet infusions per patient.

PANCREAS PROCUREMENT, TRANSPLANT ORGANIZATION, IMMUNOSUPPRESSION AND MONITORING

2.1 General schedule

2.1.1 Timing of transplantation

Like all transplants, pancreas and islet transplantations first require a pretransplant patient workup to assess benefit–risk ratio and procedural feasibility. This is followed by transplant enlistment (with an on-list waiting time of ≤ 2 years), pancreas procurement and, finally, transplantation of the whole organ or cells while following an immunosuppressant drug regimen.

2.1.2 Pretransplant workup

This workup includes an initial assessment of both hypoglycaemia unawareness and diabetes lability, plus a complete checkup for diabetes complications. Assessment for chronic infections (including dental infections and osteitis), microangiopathy and cardiovascular status (cardiac function, silent myocardial ischaemic screening, vascular Doppler monitoring) is mandatory. Cardiac ischaemic lesions should be treated before transplantation, which must be postponed for at least 6 months after an acute cardiovascular event. Assessments are similar for islet and pancreas transplants, as cardiovascular status guides both therapeutic strategies, as indicated below. Moreover, the cardiovascular risks of immunosuppressive treatment and sudden normalization of blood glucose are the same. Additional assessment of the iliac arteries is also required before pancreas transplantation. In any case, the importance of such preoperative evaluation and preparation should not be underestimated. The ideal patient for transplantation is a lean non-smoker with HbA1c levels < 9%.

The consensus statement by the European Pancreas and Islet Transplant Association (EPITA) and International Pancreas and Islet Transplant Association (IPITA) [13] defined cut-off values for beta-

cell replacement therapy as follows: HbA1c > 7.5–8%; at least one severe (requiring the assistance of a third person) hypoglycaemic episode per year; a Clarke score ≥ 4 (to assess hypoglycaemia unawareness); spending > 5% of time with hypoglycaemia < 3 mmol/L (54 mg/dL); a glucose standard deviation (SD) ≥ 40 mg/dL (2.2 mmol/L); and a coefficient of variation (SD/mean glucose) ≥ 30 with continuous glucose monitoring (CGM).

2.1.3 Principles of pancreas procurement

Transplantation requires obtaining a pancreas from an ABO-compatible brain-dead donor, while pancreases from deceased donors were authorized in April 2018. In contrast to the US and Japan, donation of an allogeneic hemipancreas from a living donor is possible, but not performed in France, as it is major surgery for the donor and increases the risk of delayed diabetes with ageing, particularly in cases of weight gain. Pancreatic harvesting requires technical specificities according to the type of transplant (isolation of the whole organ or only islets for cell therapy). Pancreases from young donors give more favourable results for all types of transplants, whereas pancreases from older patients can be used for islet isolation and are easier to achieve. The limitation of cold ischaemia duration is an important factor of success for both types of transplantation (< 11 h for whole pancreas and < 8 h for islet transplants). Graft attribution in France is done according to a priority list governed by the ABM.

2.2 Whole pancreas procurement and transplantation

The pancreas and duodenum must be rapidly dissected, with minimal mobilization and without breaching the gland capsule. The preservation solution must be extracellular (preferably fourth-generation) and contain polyethylene glycol. The pancreas is then separated from the liver, taking care that a sufficient length of portal vein is included. Preparation of the pancreas is an essential step before the graft itself. Nearly 40 different technical approaches have been described for pancreas transplantation by 121 international reference centres. In cases of SPK transplantation, the pancreas is transplanted first, using a median xypho-pubic incision and two possible routes of venous drainage: either portal or systemic *via* the vena cava; the latter is usually preferred as it is easier, whereas the

expected theoretical metabolic benefit of portal drainage has yet to be confirmed [14]. Arterial anastomosis is most often performed with the common iliac artery, provided it is not too calcified. Digestive secretions are derived from the transplanted part of the duodenum attached to the recipient's small intestine. Few centres still use bladder drainage due to the frequency of urinary complications. Post-surgical follow-up requires a stay in an intensive care unit, and the entire duration of hospitalization is 3–4 weeks.

2.3 Islet isolation and intraportal injection

Islet procurement is the same as for whole pancreas transplants, but with no vessel requirements. Islets are isolated using a slightly modified standard automated method as previously described [15], using purified collagenase before undergoing isopycnic purification in Biocoll gradients with a cell separator (Cobe 2991, Terumo BCT, Lakewood, CO, USA). Once an islet preparation isolated from a donor is deemed suitable for transplantation [containing > 200,000 islet equivalents (IEQ) and/or > 3500 IEQ/kg recipient body weight, viability > 80%, purity > 30%, volume < 8 mL], the recipient is admitted for image-guided surgical or percutaneous implantation of a silicone catheter in the portal tree under local or general anaesthesia [16]; portal pressure is controlled, and the difference between baseline and post-infusion pressures should not be > 5 cm of water. Permeability of the mesenteric and portal tree veins is controlled by Doppler ultrasound after each injection of islets.

The recipient receives one or two subsequent islet grafts as necessary. Insulin independence requires that > 10,000 IEQ/kg body mass be transplanted. The injection period is generally 3 months at the most active centres, but may be longer according to graft availability, aim of the graft (insulin independence, hypoglycaemia avoidance) and hyperimmunization. Each injection requires about 1 week in hospital.

2.4 Immunosuppressant drug regimen

IS involves two phases: an initial induction phase; and a maintenance phase throughout the entire life of the graft. Two immunosuppressive regimens are mostly used (Fig. 1). One comprises induction

with antilymphocyte serum plus a corticosteroid bolus, and maintenance with mycophenolate combined with a calcineurin inhibitor. This protocol has proven its efficacy mostly with whole organ transplants, especially kidney, liver and pancreas, with small doses of steroids often included during the first 3 months, or in the long term for pancreas transplants. This regimen can also be used for the initial injection of islets without steroid maintenance. Repeat islet injections are then supported by induction with an anti-interleukin-2 receptor antibody (anti-IL-2RA).

The first-ever published protocol for islet transplantation, the so-called Edmonton protocol, includes an anti-IL-2RA before each injection combined with sirolimus [a mechanistic target of rapamycin (mTOR) inhibitor] and low-dose tacrolimus with no steroids [1]. Also, anti-tumour necrosis factor (TNF)-alpha, pentoxifylline and antioxidant vitamin therapy are often used as adjuvant beta-cell therapy [2].

2.5 Transplant monitoring

The aim of such monitoring is to prevent rejection and recurrence of autoimmunity, using the most minimal immunosuppressive regimen, and to screen for complications and assess metabolic balance. Consistent life-long post-graft monitoring is essential, with visits approximately every week for the first month, then monthly over the first year and quarterly during subsequent years (Table I). Tests for viral serology and opportunistic infections should be performed in cases of leucopenia or other clinical signs. Abdominal computed tomography (CT) or magnetic resonance imaging (MRI) with portal vein analysis is required in cases of clinical or biological abnormalities, or according to local protocols. Pancreas graft rejection is suggested by an increase in serum lipase and confirmed by biopsy, analyzed according to Banff classification. In contrast, as islets cannot be biopsied, rejection can only be suggested by indirect markers, mainly a fall in C-peptide and the presence of donor-specific antibodies, although their pathogenicity remains questionable.

3. RESULTS AND CRITERIA FOR BETA-CELL REPLACEMENT SUCCESS

3.1. Results for insulin independence

3.1.1 Pancreas

One- and 5-year insulin-independence rates after pancreas transplantation have consistently improved in recent years. However, the fact remains that the pancreas is considered functional when no insulin is needed, regardless of HbA1c levels that may even be increased. In international registries such as the International Pancreas Transplant Registry (IPTA) [17], an analysis of 21,328 pancreas transplants performed from 1984 to 2009 (minimum 5-year follow-up) found significant improvement for both long-term patient survival and pancreas graft function. Five- and 10-year pancreas graft function rates were 73% and 56%, respectively, for SPK transplants, and 64% and 38%, respectively, for pancreas after kidney (PAK) transplants. PTA was associated with poorer results, with 5- and 10-year graft function rates of 53% and 36%, respectively (Table II). More recent 2010 and 2014 analyses of the United Network for Organ Sharing (UNOS) database showed pancreas graft survival rates reaching 89% and 72% at 1 and 5 years after transplantation, respectively [18]. From 2009 to 2015, the ABM (www.agence-biomedecine.fr) registry showed pancreas graft survival rates of 79% at 1 year and 70% at 5 years.

3.1.2 Islets

The unadjusted 5-year insulin independence rate reached 30% for islet transplantation alone (ITA) and 20% for islet after kidney (IAK) transplantation in the 2016 CITR (www.citregistry.org); however, while the 5-year results were mixed, they improved continuously over time and/or with the use of anti-inflammatory agents. Indeed, insulin independence rates (with no mention of HbA1c levels) ranged from 10–60% at 5 years in small series (10–65 patients) of either ITA or IAK transplantations, or both [19–24].

In France, the GRAGIL group published the results of patients transplanted between 2003 and 2010 with < 10,000 IEQ/kg. After 5 years of follow-up, > 60% of patients had experienced insulin independence, although < 20% remained insulin-independent [25]. However, only a few studies have reported 10-year results after ITA. In one French study, one-fourth of patients transplanted using the Edmonton protocol remained insulin-independent with HbA1c levels ≤ 6.5%, and > 70% retained graft function [4]. Type of transplantation (ITA or IAK) had no influence on the results, although primary graft function was essential for good long-term results.

3.2. Results for metabolic control and hypoglycaemia

3.2.1 Pancreas

PTA was associated with lower HbA1c levels (5.3%) and fewer cases of hypoglycaemia (7.7%) than those with failed grafts in one retrospective study [26]. Fasting glucose, 2-h plasma glucose after oral glucose tolerance test (OGTT), C-peptide and HbA1c levels were all within their normal range, with no significant differences between PTA and SPK transplantation groups at 25 ± 10 months after surgery. However, the PTA group exhibited poorer renal function and higher tacrolimus levels than the SPK group [27].

Comparison of continuous glucose monitoring profiles of T1D patients treated with either an insulin pump (n = 10) or SPK (n = 9, all insulin-independent) or IAK transplantation (n = 7, 4/7 insulin-independent) showed significantly lower mean glucose concentrations and glucose variability in SPK and IAK patients than in insulin-treated patients. In addition, mean glucose and glucose variability were similar in SPK and IAK patients, with no hypoglycaemic events in SPK patients or in insulin-independent IAK patients. Furthermore, the duration of hypoglycaemic events was significantly longer in insulin-treated than in IAK patients [28].

3.2.2 Islets

Regardless of rates of insulin independence, several non-randomized studies have shown better metabolic results with ITA than with optimal insulin therapy using multiple injections, or subcutaneous or intraperitoneal pumps with no glucose sensors [16, 28, 29]. Moreover, a decrease in hypoglycaemia was observed [24, 30], and β scores > 3 were enough to eliminate hypoglycaemia on CGM [24], and the randomized TRIMECO study confirmed these results [3]. Overall, however, a variable decline of islet function has been observed over time, leading to more rapid loss of insulin independence than of graft function, which may be preserved for > 10 years [4, 31–33], thereby allowing improvement of severe hypoglycaemia. Data from the GRAGIL network of a series of 44 (ITA and IAK) patients showed that, at 1, 4 and 5 years after ITA, 83%, 67% and 58% of ITA recipients and 80%, 70% and 60% of IAK transplant recipients, respectively, achieved HbA1c values

< 7% and were free of severe hypoglycaemia, whereas no ITA recipients and only 10% of IAK recipients met this composite criterion at the preinfusion stage [25]. One case report [33] has even described insulin independence with perfect metabolic control at 11 years after ITA. The long-term follow-up of seven Edmonton-protocol ITA patients has also been reported, although this was not an intention-to-treat analysis [32]. However, only one study [31] has reported outcomes > 5 years post-ITA, but was mainly focused on the quality of metabolic control after either simultaneous kidney–islet (SKI) or IAK transplantation.

3.2.3 Comparison of metabolic results

One study found that, 3 years after either SKI or SPK, HbA1c levels did not differ between the two groups, and both showed identical kidney function. However, insulin independence was obtained more often with whole pancreas transplantation (96%) than with ITA (31%), albeit at the cost of more adverse events (40% repeat laparotomies) [34]. In other, more recent studies, ITA results were either slightly worse or similar [4] to those of PTA, but with considerably fewer adverse events.

3.3. Criteria for successful beta-cell replacement

Up to now, ITA and PTA comparisons have suffered from a lack of consensus on the various criteria proposed to define success.

3.3.1. Insulin independence with normal HbA1c

For some authors, successful ITA is the achievement of insulin independence with normal HbA1c levels. However, it is important to first agree on the definition of insulin independence, which usually means the ability to maintain HbA1c at ≤ 6.5% with no exogenous insulin or antidiabetic treatment, deemed by the EPITA–IPITA consensus as optimal graft function [13]. Criteria for threshold values to resume insulin therapy are, however, still poorly defined. Of course, the presence of ketoacidosis or HbA1c > 7%, with a basal fasting blood glucose > 140 mg/dL and 2-h postprandial glucose > 180 mg/dL, require antidiabetic treatment. Yet, in practice, the loss of insulin independence with

detectable C-peptide (in general, > 0.5 ng/mL) when HbA1c increases to > 6.5% without insulin is considered and treated as post-transplantation diabetes until optimal insulin therapy is fully resumed with gradually increasing increments of oral antidiabetic drugs [35].

3.3.2 Composite endpoints

Other authors have defined ITA success as a composite endpoint, taking into account reductions of HbA1c and of hypoglycaemia without achieving insulin independence, and thus proposed several composite scores.

3.3.2.1 DiaCell scores

French investigators introduced the DiaCell score in 2004, which defines successful ITA as the fulfillment of four criteria: basal C-peptide ≥ 0.5 ng/mL; HbA1c ≤ 6.5%; no hypoglycaemic events; and ≥ 30% reduction in exogenous insulin [36].

3.3.2.2 β and BETA-2 scores

The β score (Table III A) was introduced by the Edmonton group in 2005, and takes into account fasting blood glucose, HbA1c, stimulated and/or basal C-peptide and use of insulin or oral hypoglycaemic agents [37]. The β score was modified as the BETA-2 score if stimulated blood C-peptide measures were not available [38]. Unlike the binary DiaCell score, the β score ranges from 0 (no graft function) to 8 (excellent graft function) with any score ≥ 6 considered a functioning graft, thereby providing an integrated measure of beta-cell graft function along a continuum that closely correlates with ITA outcomes [24]. The β score, however, does not include the incidence of hypoglycaemic events, although scores > 3 are enough to avoid hypoglycaemia. Nevertheless, it is worth noting that the only two phase-III ITA trials reported thus far had different primary endpoints: a composite endpoint of HbA1c < 7% with no hypoglycaemia in a US National Institutes of Health (NIH) trial [39]; and a modified β score in the TRIMECO trial [3].

3.3.2.3 Igls criteria

In 2017, an EPITA–IPITA workshop introduced a consensus for defining outcomes with beta-cell replacement therapy. This so-called Igls classification of beta-cell graft function (summarized in Table III B) identifies four different graft statuses (optimal, good, marginal, failure), defined according to four indicators (HbA1c, severe hypoglycaemic events, insulin or antidiabetic requirements, C-peptide) [13]. Accordingly, a graft can only be considered successful if it has either optimal (HbA1c ≤ 6.5% with no exogenous insulin or antidiabetic treatment) or good status. However, marginal function can still provide benefits to the patient by avoidance of severe hypoglycaemia or glucose variability compared with baseline status.

The workshop also introduced a clinically relevant definition of insulin deficiency, at least for T1D, based on values for fasting and stimulated (postprandial) C-peptide of < 0.3 ng/mL (0.1 nmol/L) and < 0.6 ng/mL (0.2 nmol/L), respectively. However, C-peptide monitoring requires simultaneous measurement of blood glucose and should be interpreted according to context (kidney failure, cystic fibrosis …).

Regarding hypoglycaemic events, the authors suggested following guidelines of the International Hypoglycaemia Study Group (IHSG), which takes into account so-called 'level-2' (glucose < 3 mM or 54 mg/dL) or 'level 3' (severe cognitive impairment requiring external assistance for recovery) events, as determined by self-monitoring or CGM of blood glucose [40].

3.3.3 Thoughts on these different criteria

The current French Working Group recommends adopting the EPITA–IPITA consensus guidelines that take severe hypoglycaemia into account. Nevertheless, in contrast to β (or BETA-2) scores, this is a qualitative score that has been well validated against CGM, but does not take hypoglycaemia into account. It is also worth noting that these criteria may well be changing in the near future due to the increasingly growing use of CGM. As a result, time spent within a given glucose range (70–180 mg/dL or 70–140 mg/dL and < 70 mg/dL) may soon be adopted as a surrogate for HbA1c. Recently published French recommendations for CGM in T1D patients proposed a target of 60% for time spent within the range of 70–180 mg/dL (3.9–10.0 mmol/L), with < 10% of time spent at < 70 mg/dL [41].

In addition, CGM facilitates the quantification of glycaemic variability through standard deviations (SDs) and coefficients of variation (CVs), with some authors considering variability to be excessive if the SD for glucose is > 50% or the CV is > 36%, but satisfactorily stable if the SD is < 30% [41].

4. BENEFITS

Benefits can be assessed in terms of patient survival, stabilization, and improvement in diabetes complications and quality of life.

4.1 Patient survival

4.1.1 After SPK and PTA transplantations

Survival rates for diabetes patients on dialysis is poor (30% after 3 years), and has not improved much over the years [42]. Indeed, between 2009 and 2014, the 5-year mortality rate was 61.7% in Switzerland, with 5-year survivors being significantly younger and with higher body mass index (BMI) scores [43]. In patients with T1D who can afford it, SPK is associated with a 20% gain in survival compared with kidney transplantation alone (KTA), with 10-year survival rates of 67% *vs* 46%, respectively [44]. However, patients with KTA are likely to have poorer baseline data or be ineligible for SPK, resulting in mortality data that are not exactly comparable. The patient survival rate after the first functional SPK is 90% at 72 months [17], and is similar after PAK or PTA at around 94% at 3 years. In addition, patient survival rates after pancreas transplantation have improved over time (2005–2009 *vs* 2010–2014) [17] and, moreover, preemptive SPK enables significantly better survival, considering the significant cardiovascular morbidity of these patients [45]. In fact, the 4-year survival rate in SPK patients is significantly higher than in those on the waiting list (90% *vs* 60%, respectively) [18].

Older biological age (> 44–55 years), time spent in dialysis, and the functionality of pancreas and kidney grafts are risk factors of poor survival after SPK. After PTA, past medical history and type of diabetes may also influence patient survival.

4.1.2 Post-islet transplantation

The 5-year ITA patient survival rate, as per the CITR, is close to 100%. In France, the 5- and 10-year survival rates in an intention-to-treat series of 33 patients was 97%, and did not differ significantly between ITA (100%) and IAK (92%) patients [4]. Of note, however, is the fact that IAK patients refused for whole pancreas transplantation generally had more severe complications and greater cardiovascular risk.

4.2. Diabetes complications

Each technique has proven benefits in the prevention of diabetes complications. However, the level of proof is stronger for pancreas transplants, which are most often performed in the SPK indication and therefore has the added effect of the associated kidney transplant, a long period of post-transplantation observation and a large number of patients. In contrast, few studies of ITA have recruited > 40 patients, with long-term evaluation still limited considering the recent development of the technique.

4.2.1 Pancreas

4.2.1.1 Microangiopathy

Whole pancreas transplantation leads to improvement of histological lesions and reduction of proteinuria, while creatinine clearance tends to be decreased [46]. In addition, stabilization of retinopathy has been observed at 60 months after SPK transplantation compared with non-transplanted patients with T1D [47]. Neuropathy was stabilized or improved 3 years after pancreas transplantation, with a major decrease in mortality related to dysautonomia at 5 years from 50% to 10% [48].

4.2.1.2 Macroangiopathy

Ten years after SPK, the number of cases of myocardial infarction, stroke, progressive lower-limb arteritis and amputations was significantly lower compared with KTA diabetes patients (16% *vs* 30%, respectively) [49].

Thus, in summary, successful pancreas transplantation results in well-demonstrated stabilization or

improvement of both micro- and macroangiopathy correlated with higher rates of patient survival. Nevertheless, time spent on dialysis while on the waiting list for SPK might nullify this benefit, thereby raising consideration of a living-donor kidney graft followed by secondary islet or pancreas transplantation.

4.2.2 Islets

Even before the Edmonton era, a Milanese team had already demonstrated the benefits of a functional islet graft, even if partial, performed 1–7 years after IAK transplantation, with resultant decreases in mortality, cardiovascular events and long-term deterioration of the kidney graft [50, 51]. A direct role of C-peptide levels was suggested, as HbA1c levels were apparently similar in patients with functional and non-functional grafts, at least as assessed by C-peptide levels either < or > 0.5 ng/mL. In the post-Edmonton era, various studies have focused on the consequences of ITA in terms of micro- and macrogiopathy in patients with T1D.

4.2.2.1 Microangiopathy

Renal function

In one study performed in the medium term (4 years) after ITA without a control group, the mean reduction in estimated glomerular filtration rate (eGFR) was -0.4 mL/min/month/1.73 m^2, with risk factors including long disease duration before transplantation, female gender and a history of retinopathy [52]. However, no difference was seen in a prospective study of 21 ITA patients with T1D compared with T1D patients treated with optimal insulin therapy (with similar mean eGFR reductions of -0.3 mL/min/month/1.73 m^2) [29]. Although a risk of renal graft loss or acute rejection was initially observed, most probably related to a too-sudden IS change in some IAK transplantation protocols, overall, this risk is now considered to be very low. The French–Swiss GRAGIL group showed stable kidney function 5 years after transplantation in ITA as well as IAK patients with T1D [25]. Also, 10-year results with the Edmonton protocol, which uses low-dose tacrolimus, revealed no deterioration of renal function regardless of type of transplantation [4, 53]. Moreover, stable kidney function was

demonstrated even 10 years after loss of an islet graft that had provided 1 year of insulin independence [54]. As renal complications mostly depend on the dose-dependent toxicity of calcineurin inhibitors, the type of immunosuppression used should therefore be carefully selected and adapted for each given patient.

Neuropathy

All studies [55–57] have shown significant improvements in nerve conduction velocity, especially sensory, for up to 5 years after *vs* before ITA. After ITA, however, one crossover study showed no significant improvement in nerve conduction velocities compared with intensive medical therapy [57].

Retinopathy

Several studies have evaluated the impact of ITA on progression of retinopathy. Compared with patients undergoing optimal insulin therapy, there was less worsening of retinopathy and improved retinal vascularization [29]. Also, early transient vitreous haemorrhage, which is seen after pancreas transplantation, but resolves spontaneously and is related to a sudden improvement in blood glucose levels, may arise with ITA despite careful pretransplant ophthalmological assessment [58]. Improved glucose variability appears to have a particularly favourable effect on retinal oedema.

4.2.2.2 Macroangiopathy

The few studies devoted to progression of macroangiopathy after ITA were cross-sectional studies of T1D patients with persistently functioning IAK *vs* patients with islet graft loss, PTA, KTA or treated with optimal insulin therapy. Overall survival and cardiovascular mortality rates were significantly better in those with a functional beta-cell mass for up to 7 years post-transplantation. On the other hand, the CITR shows stabilization of complications, a result that should nonetheless be interpreted with caution, as nearly 30% of patients were lost to follow-up. Carotid intima–media thickness has also been shown to improve after ITA compared with pretransplantation levels and to progress more slowly in IAK patients compared with KTA patients with T1D [59], while coronary calcifications

tended to decrease [60]. However, at this time, there are no publications evaluating acute cardiovascular events after ITA, which requires continuous long-term follow-up.

4.3 Quality of life (QoL)

4.3.1 Pancreas

QoL is significantly improved with PTA *vs* KTA patients with T1D, with a greater number of PTA patients going back to work, not missing work due to illness, and having fewer hospital admissions due to diabetes complications [61].

4.3.2 Islets

Most studies consistently show that ITA is associated with long-term QoL improvement [62, 63], related to resolution of hypoglycaemic events and the fear associated with their life-threatening risk. However, complications related to long-term diabetes and graft side-effects both have negative impacts on QoL, and become even more significant when insulin independence cannot be achieved or is lost [62, 63].

5. RISKS

5.1 Early complications related to transplant procedures

5.1.1 Pancreas

The most frequent surgical complication is portal vein thrombosis, which usually requires removal of the transplant. The proportion of pancreas loss is 8–9% in international registries and 10–15% in France [17, 18]. Other possible complications include pancreas loss related to infections, mycotic aneurysms (usually related to *Candida albicans*), pancreatitis and pancreatic or enteric fistulas. Overall, around 30% of patients require early repeat surgery. Acute rejection may also occur, revealed by abdominal pain and pancreatic dysfunction requiring steroids.

5.1.2 Islets

Percutaneous intraportal islet injections are associated with a 15% risk of serious complications, such as gallbladder puncture and haemorrhage (www.citregistry.org), and the risk is increased by the need to inject heparin [53], which has led to a switch from percutaneous puncture to mini-surgery under general anaesthesia in some centres, thereby limiting any life-threatening complications. Mini-surgery can, however, be complicated by ecchymosis, abdominal wall haematoma and intestinal occlusion, as are all surgical operations. In any case, potentially lethal complete portal thrombosis is the main risk, albeit an exceptional one. The more common partial thrombosis (2% of cases) regresses with a 3- to 6-month course of anticoagulants. Risk factors for portal thrombosis include increased portal pressure during islet injection or a high cell volume and, of course, any personal or familial history of thrombosis should prompt investigation before transplantation for potential thrombophilia. The ultimate risk is early rejection, for which there is no verified marker after ITA except C-peptide decreases.

5.2 Delayed complications of immunosuppression

IS complications include cancer, infections, and kidney and metabolic disorders, which are not specific to either PTA or ITA, but should nevertheless be carefully evaluated while bearing in mind that grafts are not as vital as other solid organ transplants, such as lungs, heart and liver. There are also the known increased risks of lymphoproliferative disorders and skin carcinomas, especially basal-cell cancer in cases of sun exposure. Calcineurin inhibitors are associated with dose-dependent renal toxicity, which can interfere with diabetic nephropathy and, thus, raise issues in terms of transplant strategies for future kidney replacement in possibly hypersensitized patients. An increased risk of post-transplantation metabolic syndrome is also well known, especially with the use of steroids or high doses of tacrolimus. The risk of diabetes recurrence is worsened by autoimmune reactivation, which is generally progressive and silent, and may precede functional decline of either pancreas or islet grafts [64], whereas alloimmune rejection can happen at any time [65].

6. INDICATIONS

Taking into account the risks of IS, it is difficult to justify either PTA or ITA in well-controlled diabetes patients with preserved renal function, although specific clinical situations may result in indications for either transplantations. Early patient referral is key for devising a strategy and adjusting treatment in a given diabetes patient. Indeed, ITA, preemptive SPK transplantation and early KTA from a living donor followed by PTA or ITA, might change the prognosis for a patient with T1D. Different strategies, depending on diabetes lability, progressive end-stage renal disease (ESRD), cardiovascular complications and sensitization, are detailed below.

6.1 Patients with renal failure

6.1.1 T1D patients with imminent or established renal failure

SPK transplantation is the most common indication, accounting for around 80% of all pancreas procedures, and should be offered to any T1D patient with imminent or established ESRD who is considering a kidney transplant in the near future (Fig. 2 A). The indication for SPK transplants could even be discussed before dialysis. In France, preemptive SPK transplantation may be offered to any patient with eGFR < 50 mL/min/1.73 m^2 (from stage 3B renal insufficiency onwards), modulated by the slope of kidney function loss (GFR $year_n$ – GFR $year_{n+1}$ ≥ 5 mL/min/1.73 m^2; normal range ≤ 2 mL/min/1.73 m^2/year after 40 years) or proteinuria > 0.5 g/day, or an albumin/creatinine ratio > 300 mg/g or 30 mg/mmol. However, the decision must weigh the expected net benefit, including renal graft survival and prevention of progression of diabetes complications, against the surgical risk generated by undergoing such a double graft [45]. Two vascular sites with no major atheroma are needed for iliac anastomosis. Patients aged < 55 years in France are usually prioritized for this type of transplant but, while those aged > 55 years have more frequent cardiovascular events than younger pancreas transplant recipients, no differences in pancreatic function have been noted in these age groups. Depending on the patient's physiological age, cardiovascular status and surgical risk, SIK transplantation or KTA followed by IAK transplantation may be preferred. In any case, a BMI < 30 kg/m^2 is required.

6.1.2 T1D patients with functional kidney grafts

For patients with T1D who have already undergone kidney transplantation and are therefore already taking an immunosuppressant regimen, two techniques are available: PAK or IAK transplantation. However, these techniques, especially pancreas transplants, should be reserved for patients with stable renal graft function who have failed to achieve good glycaemic control despite optimal diabetes management (Fig. 2 B). PAK may be proposed for patients with no cardiovascular contraindications and no atheromatosis of the iliac arteries. While there is no pretransplantation limitations for body weight and insulin dosages, obesity does increase surgical risk. IAK may be proposed for any kidney-transplant patient even without lability, as patients are already under IS, and the procedure is not as major as pancreas transplantation. In fact, the key factors for success are: no insulin resistance and, therefore, no steroid use; no rejection episodes; normal body weight; stable kidney function with no hypertension or proteinuria; and no hypersensitization. Patients with pancreases that are no longer functional or kidneys from living donors are excellent candidates for SPK transplantation. However, the little-known risk of hypersensitization may lead to decreased access to later transplantation.

6.2 Patients with labile diabetes, but no renal failure

In patients with T1D with no kidney transplant or renal failure, but with frequent episodes of severe hypoglycaemia or extreme lability despite optimal diabetes management, either PTA or ITA may be proposed, the latter being the less risky procedure (Fig. 3 A). However, given the rapid advances in insulin administration and glucose monitoring, it is difficult to define ‘optimal’ insulin therapy, which may be influenced by local resources, health insurance reimbursement and patients’ own choices. The minimum requirement is four shots of insulin with at least four capillary blood checks per day. Thereafter, different steps have been detailed in evidence-based clinical practice recommendations, with insulin pumps and sensors being the current reference modality in France [8], while the main metabolic criteria for consideration of beta-cell replacement therapy has been defined by the EPITA–IPITA consensus (see ‘Pretransplant workup’ above). The risk of degenerative complications (due to prolonged hyperglycaemia) threatening the patient’s prognosis may also be indications, as well as the patient’s clinical or personal inability to deal with hypo- or hyperglycaemia. In addition, the risk of

long-term immunosuppressant regimens must also be weighed before choosing any of these options, while the benefits of pancreas transplantation need to be balanced against the surgical risk. PTA is the preferred choice for young patients with clear iliac arteries, but at high risk of progressive diabetes complications, whereas ITA is preferentially indicated for unstable, hypoglycaemia-unaware diabetes patients free of insulin resistance and/or not overweight, yet not eligible for whole pancreas transplants according to local possibilities. Several quantitative measures of hypoglycaemia and lability are now available to facilitate assessment of instability; ITA can restore glycaemic stability even if insulin independence is not achieved and is often preferred in this indication because of its more favourable benefit/risk ratio.

6.3 Other specific situations

6.3.1 Patients undergoing pancreatectomy

Islet autotransplantation may be considered in patients undergoing pancreatectomy for chronic pancreatitis or mostly benign tumours (Fig. 3 B). In cases of ITA, the risk related to the procedure is low and no immunosuppression is required [66].

6.3.2 Cystic fibrosis patients

In patients with cystic fibrosis, simultaneous islet–lung or islet after lung transplantation may be considered (Fig. 3 B), as it may improve the risk of infections and morbidity in these patients. The procedure is currently under investigation in a clinical trial. However, the increased life expectancy for patients with cystic fibrosis is accompanied by new features of disease, particularly diabetes; this form of diabetes is promoted by altered insulin secretion due to *CFTR* gene mutations and anatomical destruction of pancreatic islets. In adult patients with cystic fibrosis and end-stage respiratory failure, lung transplants are the ultimate therapeutic options; at the lung-transplant stage, diabetes is present in half these patients, and a major factor of morbidity and mortality. Beta-cell replacement may be considered in patients with severe endocrine pancreatic disease and decreased endogenous insulin secretion and uncontrolled diabetes, despite intensive insulin therapy, whereas PTA is not indicated due to its relatively high rates of morbidity and mortality, and risk of major abdominal surgical

complications that could compromise the lung prognosis. Moreover, as ITA requires treatment for IS, which increases the risk of infection, this should be proposed only to cystic fibrosis patients with uncontrolled diabetes and end-stage respiratory failure requiring lung transplants.

Combined bilateral lung and islet grafts from the same donor are currently being studied in a multicentre French–Swiss clinical protocol using intraportal islet injection *via* a percutaneous approach under local anaesthesia. An interim analysis of the first eight patients at 1 year has demonstrated the gain of perfect glycaemic control with no hypoglycaemia and satisfactory lung function, thereby limiting the immediate post-transplant morbidity. However, patients have to continue their insulin therapy, usually at half-doses, because the number of isolated islets from a single pancreas cannot provide the insular beta-cell mass needed to achieve insulin independence. Nevertheless, pancreatic islet grafts from different donors performed 6–12 months after lung transplantation have resulted in insulin independence [67, 68], although studies in larger numbers of patients are now needed to confirm these results.

6.3.3 Other patients

Other conditions may be improved by transplantation. However, as this has not been confirmed in clinical trials, it should be discussed on a case-by-case basis.

6.3.3.1 Brittle diabetes and desire for pregnancy, especially with proteinuria

Although this has not been the subject of trials, pregnancy can be considered 1 or 2 years post-transplantation after switching from mycophenolate to azathioprine [10]. PTA is the preferred indication in cases of glycaemic lability, although patients should be informed of the potential risks of IS for the infant, which have yet to be assessed in the long term, and for the present graft and future transplants in cases of hyperimmunization.

6.3.3.2 T1D with insulin resistance or overweight

Having this condition makes surgery more difficult and could especially influence the results of ITA in cases of borderline islet mass transplants.

6.3.3.3 Maturity-onset diabetes of the young (MODY)

One study of such patients has shown good metabolic results after SPK transplantation, especially in those with MODY types 1, 3 and 5 [69].

6.3.3.4 Type 2 diabetes (T2D)

In patients with T2D, kidney transplantation may be proposed for patients with ESRD, although the indications for simultaneous or delayed pancreas transplantation are still controversial. However, SPK may be considered in T2D patients who have no signs of major insulin resistance or have intermediate forms of diabetes, yet are unable to manage multiple daily insulin infusions, or have diabetic instability.

6.4. Transplant strategies

Various factors may influence the choice of transplantation, including long-term experience with whole pancreas and kidney transplantation, which is major surgery, compared with not-as-major islet transplants, a more recent technique that has shown success in rigorous clinical trials. In any case, all transplantations require careful pretransplant workups for weighing the benefit–risk ratio of each technique.

Some criteria, such as age, BMI, blood group, human leucocyte antigen (HLA) sensitization, kidney function, proteinuria, cardiovascular status, microangiopathy and diabetes lability, depend on the patient. However, other factors, such as geographical location, ongoing clinical trials and availability of living kidney donors, are independent of the patient, yet may influence any decisions. The various factors that can affect transplant strategies are listed in Table IV, and a decision tree is depicted in Fig. 4.

In summary, PTA and combined organ transplants come with major preoperative risks, whereas ITA is easier to perform, but has to be repeated several times.

7. CONCLUSION AND FUTURE PROSPECTS

Islet transplantation has proven its long-term efficacy over the past 20 years for both alleviating the immediate burden of labile diabetes and also improving the long-term diabetes complications of T1D, with or without a kidney graft. Likewise, the results of whole pancreas transplantation have consistently improved in terms of confirmed patient survival and fewer complications. Technological approaches have also advanced during this time with the availability of CGM and 'smart' insulin pumps. The aim of the present review was to help diabetologists, nephrologists and also general practitioners offer the best and most timely treatment to patients with T1D according to their specific medical situation. In addition, it is also important to define the most commonly used tools for assessing long-term outcomes such as patient survival, metabolic results, and long-term diabetes and immune-related complications. Finally, future efforts should now focus on determining the best immunosuppressant regimes and increasing graft availability.

Figure legends

Fig. 1. The main immunosuppressive regimens used in pancreas and islet transplantation. IL2: interleukin-2; Ab: antibody.

Fig. 2. Indications for islet and pancreas transplantation in: (A) patients with insulinopenic type 1 diabetes (T1D) and renal failure; and (B) T1D patients with functioning kidney grafts. eGFR: estimated glomerular filtration rate; CGM: continuous glucose monitoring; BMI: body mass index.

Fig. 3. Indications for islet and pancreas transplantation in: (A) patients with labile type 1 diabetes (T1D) and no renal failure; and (B) islet transplantation in patients with secondary diabetes. BMI: body mass index; CGM: continuous glucose monitoring; GFR: glomerular filtration rate.

Fig. 4. Decision tree, an overview of indications for islet and pancreas transplantation. * As per glomerular filtration rate (GFR), slope of GFR decline, proteinuria criteria; # 6-month safety period; ## high with cardiopathy, peripheral vasculopathy, pneumonitis, American Society of Anesthesiologists (ASA) score > 3; § depending on daily insulin needs, body mass index; §§ consider bariatric surgery before transplant surgery; ** PAK better for long-term insulin independence and HbA1c control, IAK better for perioperative morbidity/mortality—synthesis: PAK and IAK are ± equivalents; *** SPK better for long-term insulin independence and HbA1c control, SIK better for perioperative morbidity/mortality—synthesis: SPK definitely better; **** PTA slightly better for long-term insulin independence, ITA better for perioperative morbidity/mortality, PTA = ITA for hypoglycaemia control—synthesis: ITA preferable. KTA: kidney transplant alone; PAK: pancreas after kidney; SPK: simultaneous pancreas–kidney; IAK: islet after kidney; SIK: simultaneous islet–kidney; ITA: islet transplantation alone.

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Figure 1: Main immunosuppressive regimens used in islet and pancreas transplantation

Fig 1

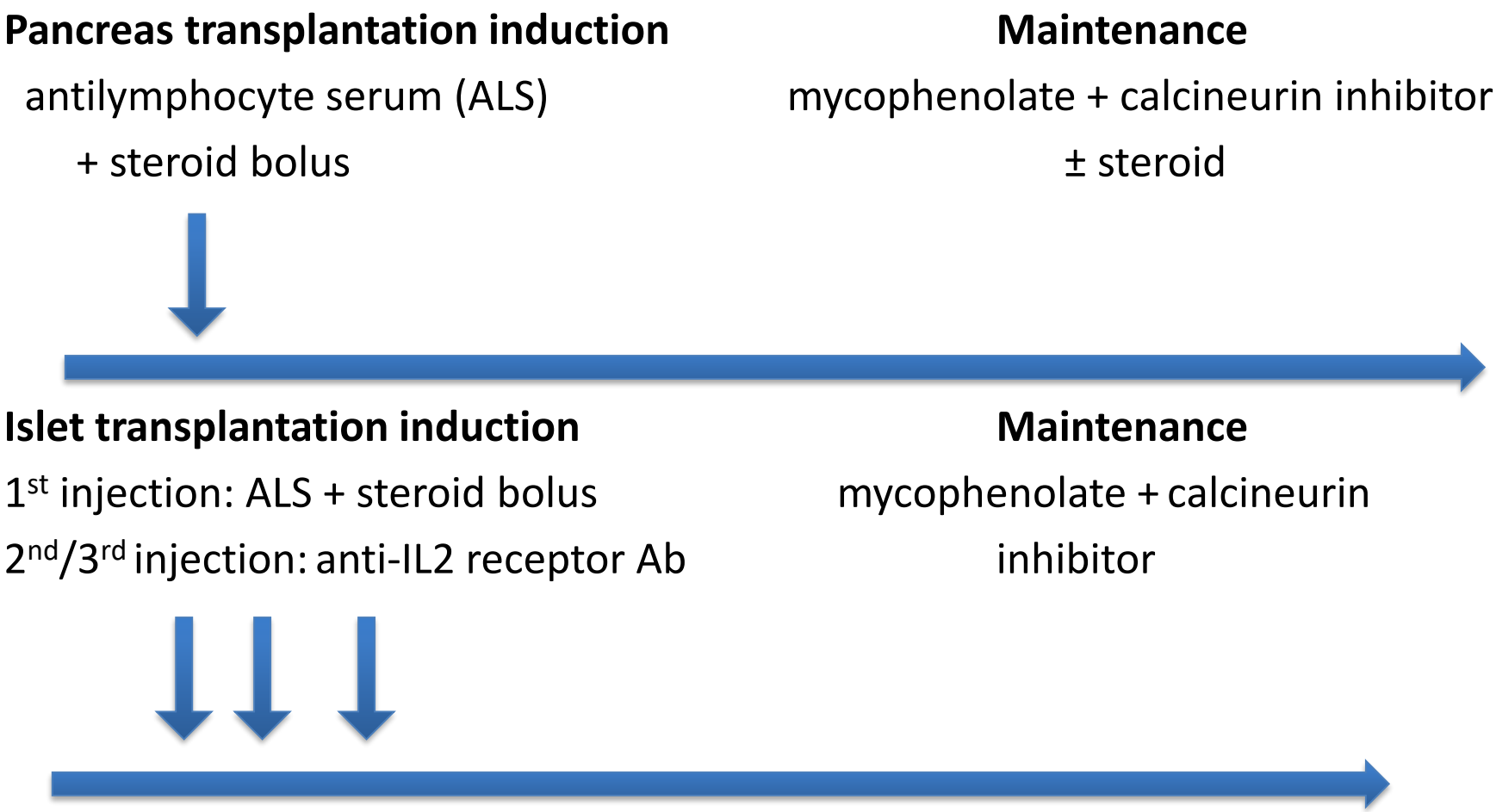

Pancreas transplantation induction
antilymphocyte serum (ALS)
+ steroid bolus
Maintenance
mycophenolate + calcineurin inhibitor
± steroid
Islet transplantation induction
1st injection: ALS + steroid bolus
2nd/3rd injection: anti-IL2 receptor Ab
Maintenance
mycophenolate + calcineurin
inhibitor
1st / 2nd/3rd injections: anti-IL2 receptor Ab
OR
calcineurin + mTOR
inhibitors

Figure 2

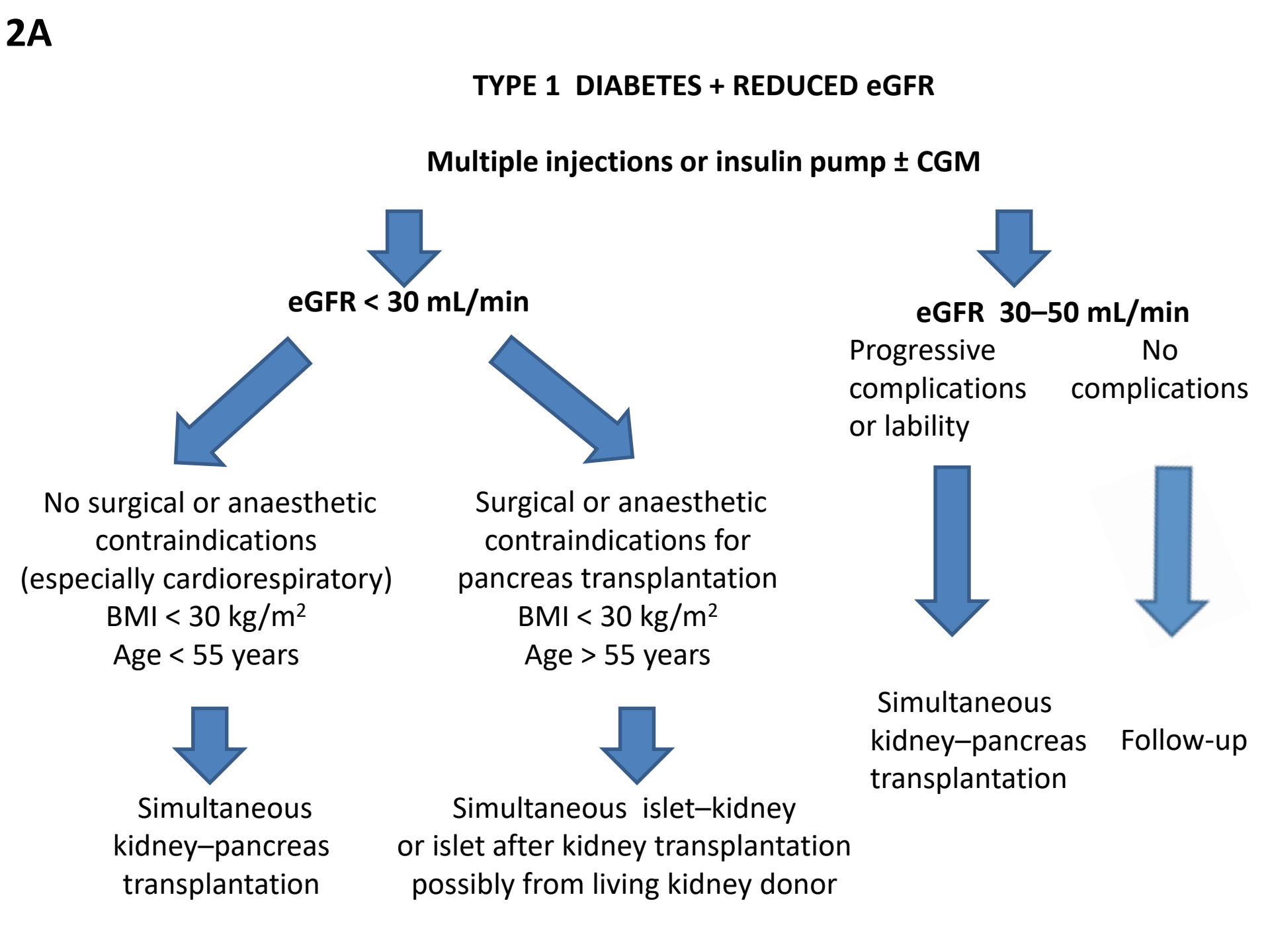
Indications of islet or pancreas transplantation in insulinopenic diabetes with renal failure

2A. type 1 diabetes with renal failure

2B. type 1 diabetes with functional kidney graft

BMI: body mass index; CGM: continuous glucose monitoring; eGFR: estimated glomerular filtration rate

2A


TYPE 1 DIABETES + REDUCED eGFR
Multiple injections or insulin pump ± CGM
eGFR < 30 mL/min
eGFR 30–50 mL/min
Progressive complications or lability
No complications
No surgical or anaesthetic contraindications (especially cardiorespiratory)
BMI < 30 kg/m2
Age < 55 years
Surgical or anaesthetic contraindications for pancreas transplantation
BMI < 30 kg/m2
Age > 55 years
Simultaneous kidney–pancreas transplantation
Simultaneous islet–kidney or islet after kidney transplantation possibly from living kidney donor
Simultaneous kidney–pancreas transplantation
Follow-up

2B

TYPE 1 DIABETES + functional KIDNEY GRAFT

HbA1c ≥ 7% or severe hypoglycaemia

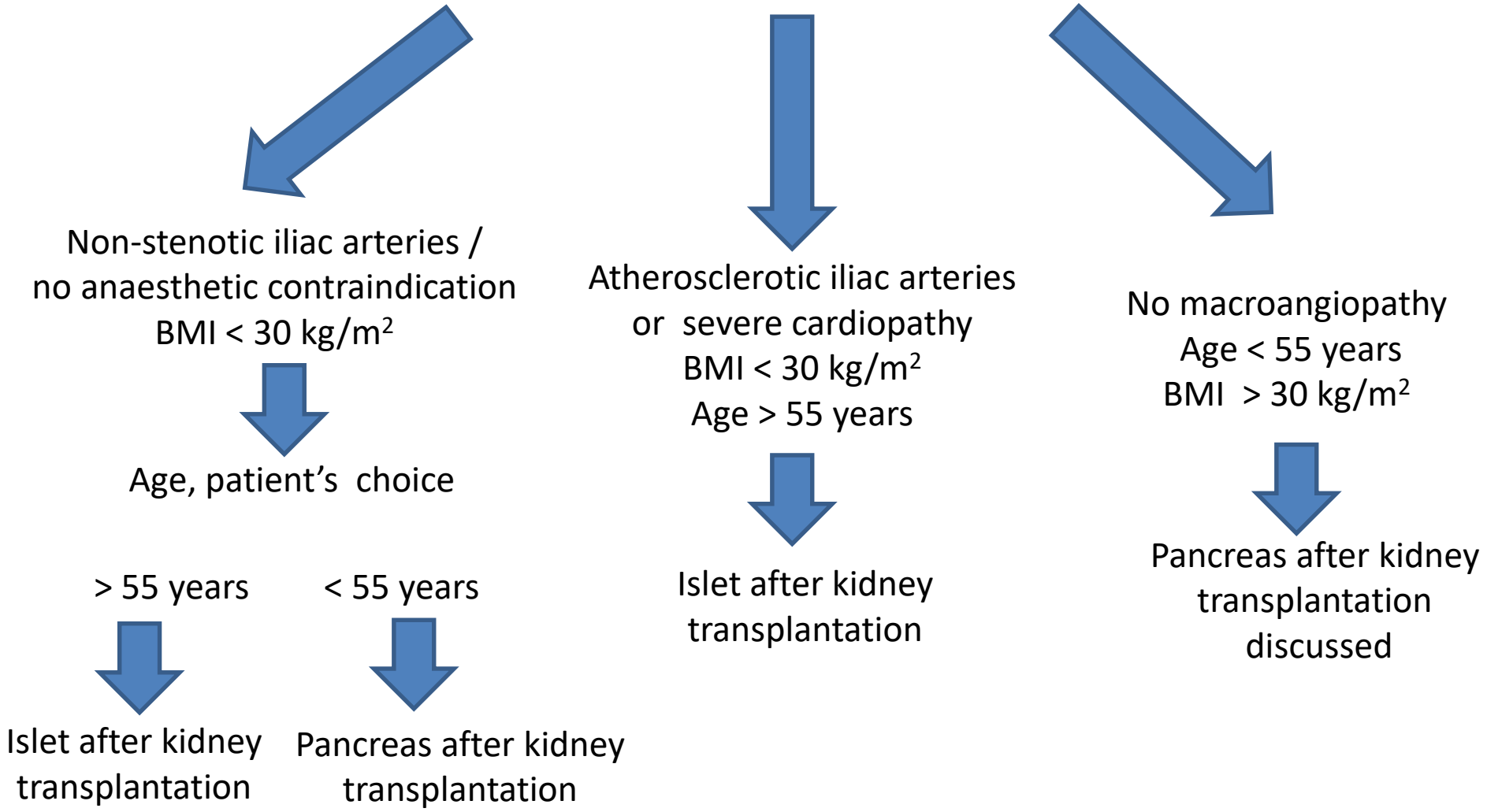


Figure 3

Indications for islet or pancreas transplantation in insulinopenic diabetes without renal failure

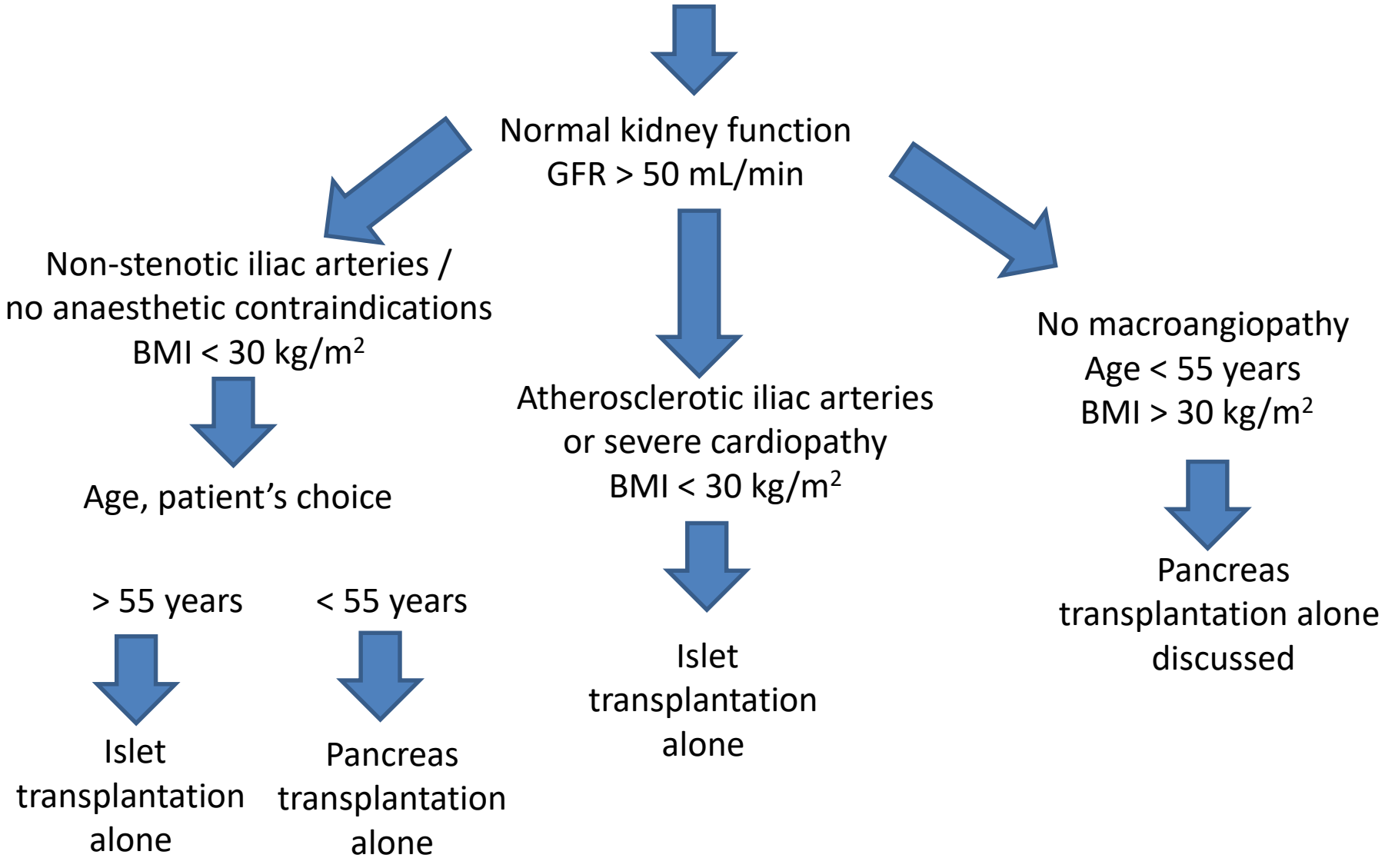
3A. type 1 diabetes without renal failure with labile diabetes

3B. islet transplantation in secondary diabetes

BMI: body mass index; CGM: continuous glucose monitoring; eGFR: estimated glomerular filtration rate

3A

TYPE 1 DIABETES
POOR GLYCAEMIC BALANCE AND/OR SEVERE HYPOGLYCAEMIA
Multiple injections or insulin pump ± CGM



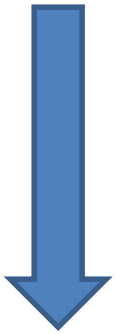
3B

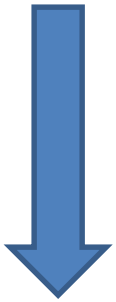
SECONDARY DIABETES

Multiple injections or insulin pump ± CGM

Post-pancreatectomy

Cystic fibrosis + end-stage organ failure
(most often lung insufficiency)





Islet
auto- or allotransplantation

Lung or other transplantation
+ islet allotransplantation

Figure 4: Overview of indications for islet or pancreas transplantation

LDKT: Live donor kidney transplant; KTA: kidney transplant alone; PAK: pancreas after kidney; IAK: islet after kidney; SPK: simultaneous pancreas-kidney; SIK: simultaneous islet-kidney; PTA: pancreas transplant alone; ITA: islet transplant alone; CKD: chronic kidney disease

£ Problematic hypoglycaemia

* Impaired kidney function according to GFR, slope of GFR decline and proteinuria criteria.

\# Safety period of 6 months following kidney transplantation.

§ Metabolic needs depending on insulin daily needs and BMI.

High surgical risk if cardiopathy, peripheral vasculopathy, pneumonitis, or ASA score > 3.

§§ Consider bariatric surgery before pancreas transplantation

** According to patient's choice:

PAK is better in terms of long-term insulin independence and control of HbA1c

IAK is better in terms of peri-operative morbidity-mortality

--> Synthesis: PAK and IAK are +/- equivalents.

*** According to patient's choice:

SPK is better in terms of long-term insulin independence and control of HbA1c

SIK is better in terms of peri-operative morbidity-mortality

--> Synthesis: SPK is definitely better.

**** According to patient's choice:

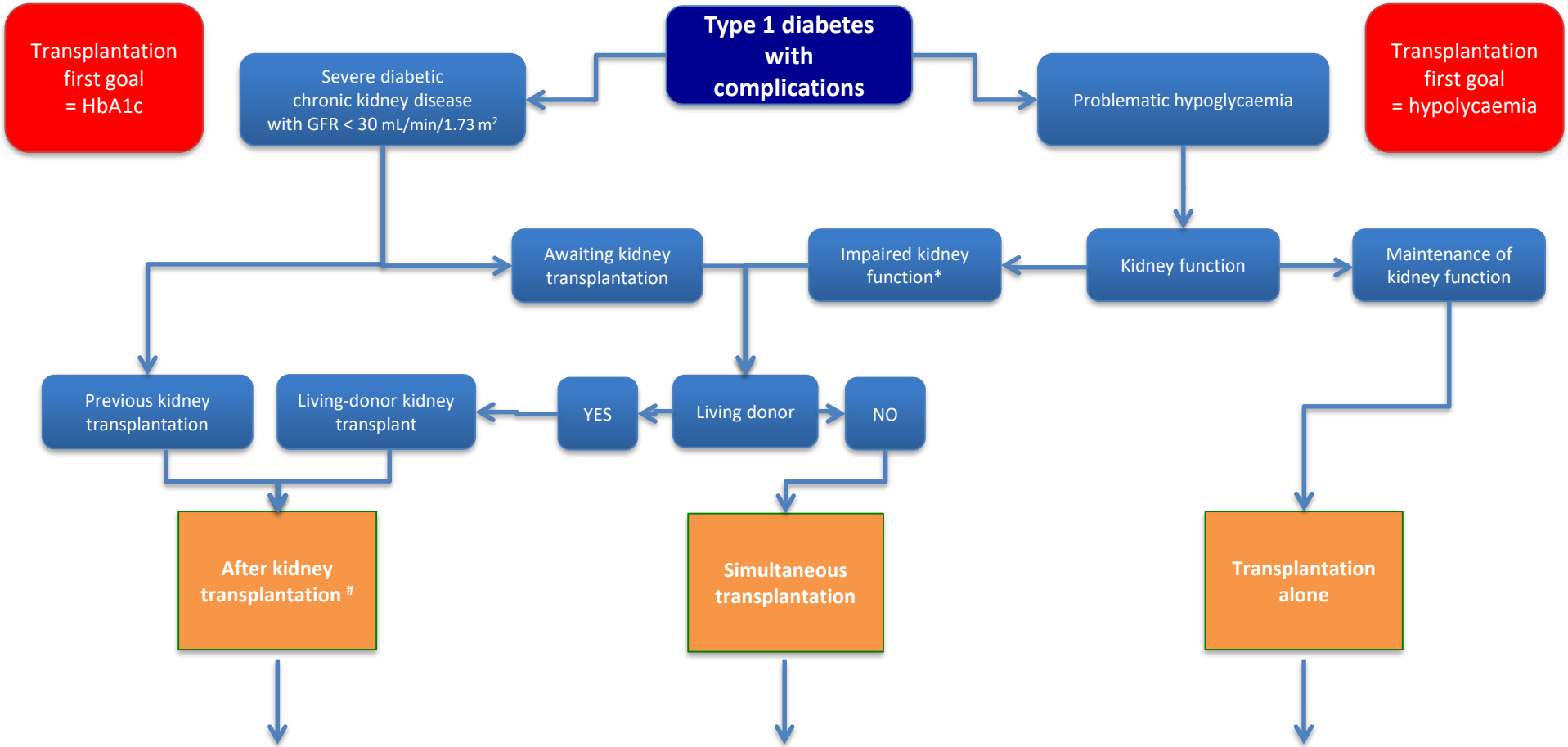
PTA is slightly better in terms of long-term insulin independence

ITA is better in terms of perioperative morbidity-mortality

PTA and ITA are equivalent for the control of hypoglycaemia

--> Synthesis: ITA preferable

4



Metabolic needs § \ Surgical risk ##	High	Low
High	KTA	PAK §§
Low	IAK	Patient's choice **

Metabolic needs § \ Surgical risk ##	High	Low
High	KTA	SPK §§
Low	SIK	Patient's choice ***

Metabolic needs § \ Surgical risk ##	High	Low
High	?	PTA §§
Low	ITA	Patient's choice ****

Table I: Islet and pancreas monitoring

PARAMETERS
General Blood cell count Kidney function: creatinine, glomerular filtration rate, microalbuminuria, proteinuria, haematuria Liver function: liver enzymes, bilirubinaemia Pancreatic exocrine function: lipase
Metabolic Fasting and stimulated blood glucose C-peptide HbA1c
Immunological Blood trough immunosuppressant drug measurements Alloimmunity: anti-human leucocyte antigen (HLA) antibody Autoimmunity: glutamic acid decarboxylase, islet cell, tyrosine phosphatase antibodies
SCHEDULE
Weekly visits for first month Monthly visits for first year Quarterly visits for subsequent years + continuous glucose monitoring, oral glucose tolerance test once a year

Table II
Patient and graft survival (defined as insulin independence unless otherwise indicated) after pancreas and islet transplants during 2005–2014 [18] and since 2003 for islet transplants [4]

SURVIVAL	PATIENTS		GRAFTS	
	5-year	10-year	5-year	10-year
Pancreas–kidney transplantation				
Simultaneous	90%	67% (*vs* 40% on dialysis	72%	56%
Pancreas after kidney	–		64%	38%,
Pancreas transplantation alone	90–94%		53%	36%
Islet transplantation alone	100%	100%	30% (CITR) 50% (Lille)	20–25% (Lille) 70% C-peptide +
Islet after kidney transplantation	92%	92%	20% 50% (Lille)	20–25% (Lille) 70% C-peptide +

CITR: Collaborative International Transplantation Registry

Table III
Assessment of graft function by (A) β, (B) Igls and (C) BETA-2 scores

A

Score	**2**	**1**	**0**
Fasting glycaemia (mmol/L)	≤ 5.5	5.6–6.9	≥ 7.0
HbA1c	< 6.1	6.2–6.9	≥ 7.0
Daily insulin needs (IU/kg)	0	0.01–0.24 and/or OADs	≥ 0.25
Stimulated C-peptide (nmol/L)	≥ 0.3*	0.1–0.29	< 0.1**

* Fasting blood C-peptide ≥ 0.3 nmol/L (1 ng/mL); ** β score is 0, range: from 0 (no) to 8 (excellent) graft function;
OADs: oral antidiabetic drugs

B

Functional status	**HbA1c (%)**	**SH events**	**Insulin needs (IU/kg/day)**	**C-peptide**	**Success**
Optimal	≤ 6.5	None	No	> Baseline	Yes
Good	< 7.0	None	< 50% Baseline***	> Baseline	Yes
Marginal	≥ 7.0	< Baseline*	≥ 50% Baseline	> Baseline	No*****
Failure	Baseline	Baseline**	Baseline	Baseline****	No

* If severe hypoglycaemia (SH) present before β-cell therapy, then continued benefit may require assessment of SH exposure (< 3 mmoL), hypoglycaemia awareness, glycaemic variability/lability;
** If SH not present before β-cell therapy, then return to baseline is indication for treatment;
*** May include use of non-insulin antihyperglycaemic agents;
**** Not reliable in uraemic patients with evidence of C-peptide production prior to β-cell therapy;
***** Clinical decision still needed if benefit of maintaining/monitoring β-cell graft outweighs risk

Table IV

Factors modifying indications for whole pancreas and islet transplantation

FACTORS	CONSEQUENCES
Age	Consider physiological rather than 'absolute' age, especially cardiovascular status; Older patients (> 40 years) have better results with ITA; Younger patients (< 55 years) often better tolerate major surgery, such as PTA; Wish for pregnancy should postpone ITA, unless life is threatened
Body mass index (BMI)	Should be < 30 kg/m^2; Lower BMI (and daily insulin needs) more suitable for ITA; May negatively impact prognosis for PTA
Smoking	Should be stopped
Blood group	All transplants are performed according to ABO compatibility with negative cross-matching; B and AB groups are rare, so may increase time on waiting list
Sensitization	Detectable HLA autoantibodies generally appear after pregnancy or transfusion as factors of poor post-transplant outcomes, especially if PRA rate is > 20%; Recommend simultaneous pancreas–kidney transplant as only a donor is required; Mean fluorescence intensity (MFI) antigen levels > 3000–5000 should be forbidden
Kidney function	For proteinuria or rapid decline in glomerular filtration rate (GFR), preemptive simultaneous pancreas–kidney transplantation is recommended
Macroangiopathy	If present, islet transplantation is recommended
Microangiopathy	Must be stabilized before any transplant surgery, especially retinopathy
Brittle diabetes	Recommend transplantation, especially ITA if no end-stage renal disease (ESRD)
Patient's choice	Should be taken into account, as with desire for pregnancy
Local resources	If no contraindications, local possibility of ITA or PTA may guide choice
Living kidney donor	In ESRD, living donors favour KTA, followed by ITA or sometimes PTA
Associated autoimmune diseases	Not contraindicated except if treated with steroids; May improve with immunosuppression
Associated grafts	Kidney graft: good indication for ITA, especially if previous pancreas graft after SPK transplantation is lost; Lung transplant: ongoing protocol for cystic fibrosis; Liver transplant: theoretically not a contraindication, but should be discussed
Preemptive transplantation	Should be considered for any T1D patient with GFR > 15 but < 50 mL/min/1.73 m^2 ± proteinuria: SPK associated with better survival, QoL (dialysis avoidance, insulin discontinuation), but graft prognosis related to stabilization of diabetes complications, less cardiovascular morbidity (especially related to arteriovenous fistula), less HLA sensitization *vs* those transplanted after beginning dialysis, after living donor kidney transplant or still on the waiting list.

ITA/PTA: islet/pancreas transplantation alone; HLA: human leucocyte antigen; PRA: panel reactive antibody; KTA: kidney transplantation alone; SPK: simultaneous pancreas–kidney; QoL: quality of life