he field of β-cell replacement therapies has evolved substantially over the last decades. The lesson learned from recent islet transplantation trials in patients with unstable type 1 diabetes is that primary goals are the achievement of stable, normalized glycemic control in the absence of severe hypoglycemic episodes with improvement of quality of life and the prevention of progressive, chronic diabetes complications. Insulin independence, although desirable, should not be considered the main objective, particularly in light of the sustained positive effects achieved even with a “marginal” functional islet mass via restoration of C-peptide secretion and reduction of insulin requirements. As present limitations of islet transplantation are progressively overcome, the clinical application will greatly expand from the currently limited indication in controlled clinical research trials to more widely available cellular therapies and regenerative medicine solutions that will eventually be offered as standard treatment to the majority of patients with insulin-requiring diabetes.

Vantyghem et al. (1) in the article in this issue of Diabetes Care evaluated the predictive value of primary graft function on long-term clinical outcomes of islet transplantation alone (ITA). Surrogate measures have been proposed to monitor or predict β-cell function, but they are not yet fully validated (2–4). In this report, the use of the β-score in the early post-transplant period allowed to quantify primary graft function that, when “optimal,” was associated with prolonged graft survival and better metabolic control following islet transplantation (1). In agreement with previous reports using the “Edmonton Protocol” (5–10), this trial resulted in a significant improvement of metabolic control and long-term graft function (~70% having measurable C-peptide at 5 years). Importantly, the investigators also showed prolonged insulin independence in 57% of the patients at 5 years, with the subjects with optimal primary graft function exhibiting the highest success rates (~70% insulin free and 100% of functioning grafts >4 years) (1). Similar long-term insulin independence rates have been reported using novel protocols based on lymphodepleting agents in combination with maintenance immunosuppressive regimens minimizing β-cell toxicity that have shown sustained insulin independence for >3 years (~60%) (9) and even at 5 years (~50%) (11). Collectively, these encouraging results indicate that ITA may lead to long-term insulin independence rates that are comparable to those of pancreas transplant alone (~60% at 5 years) (12) and justify the need for reassessment of islet transplantation as clinical option for β-cell replacement.

The treatment of choice for patients with type 1 diabetes consists of exogenous insulin therapy with tailored diet and physical exercise (13). The importance of achieving tight glycemic control has been well established (13,14). Intensive insulin therapy can delay the onset and reduce the progression of chronic diabetes complications (14), but unfortunately, it is associated with a significantly increased number and severity of hypoglycemic episodes (1,5), particularly in patients with long-standing diabetes with autonomic neuropathy and hypoglycemia unawareness. Indeed, the risk of experiencing severe hypoglycemia is significantly higher under intensive insulin compared with conventional regimens (relative risk to experience ≥1 episode = 3.28) with the same individual being at higher risk for multiple episodes (22% of subjects with ≥5 episodes vs. 4%, respectively) (15).

Tight glycemic control throughout the day still remains difficult to attain using conventional insulin therapy, and the risk for long-term diabetes complications has not completely been eliminated. The use of novel insulin formulations, infusion pumps, and glucose monitoring systems has substantially improved diabetes care in recent years, contributing to a significant amelioration of quality of life and to the reduction of chronic complications and of side effects associated with conventional insulin therapy in patients with type 1 diabetes. Patients with erratic daily glycemic excursions, progressive complications, and hypoglycemia unawareness are highly susceptible to multiple severe hypoglycemic events, at times life-threatening. Attaining stable metabolic control in this brittle patient population is of utmost importance also in view of the significant mortality rate in such subjects, with apparently normal renal function, while waiting for a pancreas transplant (~8% at 4 years for pancreas transplant alone) (16). Thus, medical therapy cannot attain the desirable therapeutic efficacy in such a selected population of subjects with type 1 diabetes.

Restoration of β-cell function is a highly desirable goal for patients with unstable type 1 diabetes. β-Cells are highly specialized glucose sensors able to secrete insulin in “real time” to finely regulate glucose homeostasis. Indeed, physiological metabolic control is attained after transplantation of pancreatic islets either as isolated cell clusters or as vascularized pancreas organ. Pancreas transplantation, despite improving glucose control, chronic complications, and quality of life and having long graft function and survival, still has a relatively high perioperative mortality and morbidity and specific limitations (12,16). Alternatively, allogeneic pancreatic islet transplantation can be an attractive, minimally invasive, and safer option for this group of patients with unstable type 1 diabetes, by inducing restoration of physiological glucose sensing and insulin delivery. Islet transplantation occurs by gravity infusion of the heparinized islet product from a closed-bag system via microembolization into the hepatic portal venous system, with the islets entrapping in its peripheral branches, at presinusoid level because of the size restriction followed by their engraftment and neovascularization from the hepatic vasculature, with instant function and survival. This interventional radiology procedure is performed by percutaneous transhepatic catheterization of the main portal vein branches under fluoroscopic and ultrasound guidance with local anesthesia and conscious sedation and with close monitoring of portal pressure; it
lasts ~1 h, and allows patient discharge from hospital within 48 h, once clinically stable and without complications (6,17).

Clinical trials in the 1980s and 1990s were performed in islet-after-kidney (IAK) and simultaneous islet-kidney (SIK) transplantation recipients using corticosteroids and high-dose calcineurin inhibitors (CNI) or purine antagonists (8,17). Such protocols were mainly focused on preserving the kidney graft function and were associated with diabeticogenic effects. Clinical outcomes were overall poor, with many cases of primary graft nonfunction, low rates of insulin independence at 12 months (~10%), and limited graft survival. Steady progress in islet cell processing, novel immunosuppressive strategies, and improved patient management have led to increasing success rates of islet transplantation in the last 30 years (17). In the late 1990s, the introduction of a steroid-sparing immunosuppressive protocol (the Edmonton Protocol), consisting of an induction with anti-CD25 antibody and maintenance with low-dose CNI and high-dose mTOR inhibitors, resulted in sustained (>12 months) insulin independence in recipients of sequential ITA (18). This approach has proven reproducible (even with some modifications) and also applicable for SIK and IAK transplants (1,6—10,19—21).

Collectively, ~650 islet transplants in 325 recipients have been reported since 1999 by the Collaborative Islet Transplant Registry (CITR) (22). Common achievements of these studies are the improved glucose control and the reduction of insulin requirements with normalization of A1C as well as absence of severe hypoglycemia, even in patients with partial graft function requiring exogenous insulin. Islet transplantation is also associated with a significant improvement of quality of life that parallels the positive metabolic effects together with prevention of severe hypoglycemia and restoration of hypoglycemia awareness (8,23). Insulin independence is usually obtained when adequate islet numbers, generally from two or more donor pancreata, are transplanted (i.e., ~10,000—14,000 islet equivalents per kilogram of recipient's body weight). The rate of insulin independence at 1 year is ~70% (and even higher in the most experienced centers), with virtually all patients maintaining a functioning graft (positive C-peptide), while under adequate immunosuppression levels (1,6—10,19—21). Similar results have been replicated in a small series of single-donor ITA receiving lower (marginal) islet masses (~<10,000 islet equivalents/kg body wt) while using specific lymphodepleting and anti-inflammatory treatments at induction and conversion to CNI-free maintenance therapy, which included the purine synthesis inhibitor mycophenolate acid (19,20). As a result of fewer systemic and β-cell negative side effects, current islet transplantation studies increasingly include this drug in their maintenance regimen.

Following islet transplantation, physiological β-cell response to secretagogues is restored to a certain extent, including improved first-phase insulin secretion upon intravenous stimulation and increased overall C-peptide levels following oral challenge (3). As mentioned, the neurohormonal and symptomatic responses to hypoglycemia (e.g., glucagon and epinephrine) are altered in patients with type 1 diabetes. Although an initial report suggested that intrahepatic islet transplantation did not restore hypoglycemia hormonal counterregulation and symptom recognition (24), more recent studies have shown normalization of the glycemic thresholds for activation of counter-regulatory hormone and symptom responses to hypoglycemia, though the magnitude of such responses remained impaired (25,26). Glucagon secretion was also normally suppressed by hyperinsulinemia in these patients (25). It is conceivable that all the above-mentioned phenomena contribute to the observed posttransplant improvement of metabolic control and to the restoration of hypoglycemia awareness after islet transplantation (27).

Overall, sustained graft survival is achieved in the majority of islet transplant recipients, with ~70% of them retaining C-peptide levels, normalized A1C, nearly absent severe hypoglycemia, and significantly reduced insulin requirements (~<50% from pretransplant dose) at 5 years under the Edmonton Protocol (1,5). Notably, both the improvement in quality of life and the restoration of hypoglycemia awareness persist long term (23,27). However, the rate of insulin independence may progressively decline after transplantation, reaching ~10% at 5 years despite maintaining islet graft function (5).

Recent trials have generally relied on the use of multiple donor islets to attain insulin independence. The number and quality of islets obtained from a donor pancreas remain quite variable, and <50% of glands processed with the intent to transplant yield adequate islet numbers (28). The success rate of islet isolation improves (~≥60%) when organ recovery is performed by a local team involved with the transplant program (28). In an attempt to minimize competition with vascularized pancreas transplantation, islet transplant programs are generally offered pancreata that have previously been offered and turned down for whole organ transplant as well as glands obtained from older and obese donors that are considered less than optimal for surgical implant (29,30). Notably, this pancreas allocation scheme does not account for potential limitations in islet potency and longevity of such organs that could negatively affect long-term outcomes of islet transplantation (30). Notwithstanding the steady increase in organ donation, pancreas recovery rates remain unsatisfactory and much lower than those for other solid organs; e.g., ~>8,000 multiorgan donors were available through the United Network for Organ Sharing (UNOS) in 2006 (of these, ~2,000 pancreata were recovered and only ~1,440 used for transplant [http://optn.transplant.hrsa.gov/data/annualReport.asp]). In the period 2000—2004, the poor utilization of potential islet donor pancreata was recorded in the U.S. (30). In particular, from the overall pool of pancreata available, 22.3% (“optimal” glands) were used for whole organ transplant; from the remaining pool, 48.5% were considered “suitable islet donors” (11% “optimal” and 89% “standard”), but only 2.1% of them were actually used for islet transplantation (30). Therefore, a wide margin for improvements in organ allocation and utilization exists that include the use of “optimal” donors and a fair allocation between islets and whole pancreas transplant programs. In addition, changes in the current cost structure of pancreas procurement, which differentiate the payment based on the transplant suitability of the islet tissue products (determined after completion of the manufacturing process) rather than based on the acceptance of whole organ transplantation, will help reduce the overall economic burden of islet transplantation (31). In light of the promising results obtained with single-donor marginal islet mass infusions, when adequate donor-organ selection and targeted recipient immune interventions are implemented (20), the number of islet transplants could be substantially improved with the cur-
rently available donor pool and potentially satisfy the demand for the relatively con-
tained targeted population that would greatly benefit from islet transplantation.

Type 1 diabetes–related micro- and macrovasculopathy are the main causes of
chronic end-stage renal disease (ESRD) requiring dialysis, blindness, and limb
amputations and deformities, with associ-
ated disabilities, comorbidities, and death (32). Their impact is ~10% of the
total health care expense in western coun-
tries, with >100 billions USD spent every
year in the U.S. alone and >200 billions
USD worldwide (32). Stabilization or re-
duction of the progression of retinopathy
and neuropathy has been reported after
islet transplantation (33). In IAK recipi-
ents, improvement of cardiovascular and
endothelial function, amelioration of the
atherothrombotic profile, and reduction of
cardiovascular events with better pa-
tient survival rates have been reported
when compared with those of recipients of
renal transplant alone (90% at 7 years
vs. 50%, respectively) (34,35). In addi-
tion, the longevity of the concomitant re-
nal allograft appears to be significantly
prolonged following the achievement of a
better metabolic control associated with
islet transplantation (36), although addi-
tional factors (i.e., better organ quality of
the kidney grafts transplanted in recent
years) also significantly contribute to such
improvements (37).

The restoration of C-peptide produc-
tion following islet transplantation may
also contribute to some of the improve-
ment of diabetes complications observed
posttransplant. Indeed, putative mech-
nisms accounting for the possible benefi-
cial effects of C-peptide include reduction of
delayed hypoglycemia and increased
myocardial and renal blood flow as well as in
peripheral vascular districts and tissues
(i.e., skeletal muscle), as suggested from
studies in subjects with long-standing
type 1 diabetes receiving C-peptide infu-
sion. These events, in turn, may contrib-
ute to improve cardiovascular and renal
function, thus possibly reducing the pro-
gression of diabetic angiopathy and re-
lated complications (38).

A current hurdle to more widespread
use of islet transplantation includes the
need for chronic immunosuppression and
its associated untoward side effects.

The rate and type of immunosuppression-
related complications observed in islet
transplant recipients under the Ed-
monton Protocol are not different from those
reported in solid organ transplants
(mainly opportunistic infections and
drug-related toxicity) and were expected
based on the pharmacological profile of
the current immunosuppressive agents
(39). From data of more than 300 islet
recipients during ~10 years of monitor-
ing, procedure- and infusion-related seri-
ous adverse events (e.g., abdominal
bleeding) were extremely rare (<6% in
the 1st year), with only 2 of 111 cases
that were not fully resolved. Novel radiolog-
techniques, intracathether tract coagu-
lants, and recipient peritransplant
antithrombotic prophylaxis have signifi-
cantly reduced their occurrence (22).
Regarding immunosuppression therapies,
despite common infections (e.g., skin and
urinary tract) and direct drug effect (e.g.,
myelodepression and gastrointestinal dis-
tuors), only 96 serious adverse events
possibly or definitely related to immuno-
suppression have been reported, with 82
resolved with no sequelae, 17 with se-
quelae, 6 with persistent condition, and
only one death (viral meningitis). Six
other deaths were reported not directly
related to the islet transplant or its medica-
tions. Neoplasms occurred in 14 islet
recipients, but just 4 were possibly related
to immunosuppression (squamous and
basal cell skin cancers, papillary thyroid
carcinoma, and ovarian cysts) (22).

The negative effects of CNI and
mTOR inhibitors on renal function have
been widely recognized. The potential
negative impact of these drugs on the
progression of diabetic nephropathy in
nonuremic subjects needs to be fully eva-
luated. In the context of islet transplanta-
tion, decline of renal function has been
reported in some studies (7,40,41),
whereas more recent reports have
described stable renal function and lack of worsen-
ing of diabetic nephropathy in long-term
follow-up (8,42,43) or an initial decline of
renal function that stabilizes without
further worsening in the long term (9).
Notably, strict selection of islet transplant
candidates without previous renal dys-
function (i.e., microalbuminuria and low
estimated glomerular filtration rates) and
timely implementation of nephroprotec-
tive and antihypertensive therapies (i.e.,
inhibitors and/or angiotensin receptor
blockers) may have accounted for the
different clinical outcomes (43). Immu-
nosuppressive protocols void of nephro-
toxicity are highly desirable; indeed,
ongoing clinical trials are showing promi-
sing results in patients undergoing con-
version of either CNI or mTOR inhibitors
to mycophenolate acid maintenance, with
preservation of both renal and islet func-
tion (8,9,42,43).

Several factors may contribute to the
progressive islet graft dysfunction and
failure observed over time under the Ed-
monton Protocol in addition to the recipi-
ent immune response. After an initial
islet mass loss following the intraportal
infusion, as a result of an instant blood-
mediated inflammatory reaction and the
deleterious graft hypoxia until engraft-
ment and neovascularization, the intrahe-
patic islets are chronically exposed and
damaged by the high levels of lipids, glu-
cose, and immunosuppressive drugs and
by the local inflammatory milieu (44).
Direct B-cell toxicity and functional impair-
ment consequent to exposure to CNI have
been widely recognized. Experimental evi-
dence supports the antiproliferative ef-
ccts of mTOR inhibitors and CNI that
may result in impaired islet engraftment
(i.e., altered neovascularization and tissue
remodeling) and reduced B-cell self-
renewal (45). Additionally, increased
lipid levels are commonly associated with
immunosuppression (mainly mTOR in-
hibitors) and may result in B-cell lipoto-
xicity contributing to loss of functional islet
mass over time (39).

Reproducible, single-donor islet
transplantation is indeed a highly desir-
able goal (20). This is particularly impor-
tant considering the risk of recipient
sensitization to donor alloantigens that
is an expected finding following solid organ
transplantation (46 – 48). Islets from
HLA-mismatched, ABO compatible do-
nors are used (with the exception of SIK
recipients) in an attempt to minimize the
risk of recurrent autoimmunity. Adequate
immunosuppression in islet transplant
recipients appears to prevent the develop-
ment of alloantibodies and to neutralize
their potentially negative impact on graft
survival, even in the presence of low
degree of panel-reactive alloantibodies
pretransplant (47,48). Nevertheless,
posttransplant development of donor-
specific and non–donor-specific alloanti-
bodies may be detected after drug dose
reduction (i.e., for medical reasons),
while it invariably occurs when immuno-
suppression is withdrawn (i.e., at islet
graft failure) (47,48). Although the signif-
ificance of this phenomenon and its poten-
tial impact on long-term islet graft
function or subsequent allografts have not
been established, there is a concern for
potentially limiting future therapeutic op-
tions (i.e., subsequent islet, pancreas, or
renal transplantation for ESRD) (47). Se-
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lection of subjects with slow progression of diabetic nephropathy who will unlikely develop ESRD as well as attempting more stringent donor-recipient HLA matching may contribute to reduce the risk of allosensitization in islet transplant recipients (43). It is conceivable that development of tailored immunosuppression weaning protocols after islet graft loss may be of assistance in reducing the risk of allosensitization.

Persistence or recurrence of autoimmunity has been described in islet transplant recipients and has been associated with lower rates of insulin independence and shorter graft survival (49). Selective destruction of β-cells within islet allografts by histopathology analysis, measurable changes of autoantibody levels (i.e., anti-GAD65 and anti-insulinoma-associated protein 2), and/or detection of autoreactive cytotoxic and memory T-cells to β-cell–specific epitopes have been described (50). A close monitoring of immune activation and β-cell function markers during the follow-up may be of assistance in detecting early islet graft distress and possibly guide timely therapeutic interventions (i.e., metabolic support or immunotherapy) to preserve islet mass long term (10). This has been shown, for instance, with the use of exenatide to preserve islet function after detection of graft dysfunction (51).

Overcoming the current challenges of islet transplantation requires a sequential, integrated approach aimed at enhancing the yield and quality of islet cells from a single-donor pancreas, as well as improving the survival and function of the transplanted islets using safer and more effective cytotoxic and immunomodulatory approaches (17,44). Increased islet yields have been obtained using more efficient pancreas recovery and preservation as well as islet isolation and purification strategies (17,44). Peritransplant interventions aimed at reducing inflammation and conferring cytoprotection to islet cells (i.e., reducing β-cell death) have shown promise in enhancing engraftment and improving long-term outcomes. In the clinical setting, tumor necrosis factor-α blockade enhances islet engraftment and survival (6,20,22). Similarly, glucagon-like peptide synthetic analogs (i.e., exenatide) have been introduced to enhance β-cell function and possibly survival after transplantation, with encouraging results in patients with suboptimal islet masses both at the time of the islet transplant and after development of graft dysfunction (51,52). Translational experimental models have provided evidence that cytoprotective agents (e.g., lisofylline, caspase and Jun NH₂-terminal kinase inhibitors) not only reduce islet cell loss but also may favor the efficacy of tolerogenic protocols by modulating local inflammation and immune responses (44,53,54). Although current immunosuppressive agents prevent rejection via nonspecific antiproliferative effects, this has a costly trade-off in terms of untoward side effects, including organ and β-cell toxicity. Compared with standard protocols, powerful lymphodepleting induction agents (i.e., thymoglobulin, anti-CD52, anti-CD3, and anti-CD20 antibodies) are showing promising results in terms of safety profile and improvement in islet graft function (19,20,55,56). Immunomodulatory agents, selectively targeting costimulatory signals of T-cell activation and/or adhesion molecules, are becoming available for clinical applications and may have relatively lower side effects and islet or organ toxicity (i.e., lack of diabetogenicity and nephrotoxicity) as well as possibly promote immune tolerance in specifically designed protocols (57). Many of the above-mentioned agents are currently under evaluation in the National Institutes of Heath (NIH)–sponsored Clinical Islet Transplantation (CIT) Consortium (www.citisletstudy.org) carrying on phase II-III randomized ITA and IAK tria ls both in North America and Europe. Primary objectives of the CIT trials are the confirmation and improvement of the success rate of islet transplantation and the standardization of the isolation and transplant procedures, toward approval of islet transplantation as standard of care, reimbursable by health insurance.

Attempting to induce immune tolerance to the transplanted tissues is an appealing perspective for islet transplantation (57). There is an increasing body of experimental data supporting the value of adjuvant cellular transplants (i.e., bone marrow–derived cells, mesenchymal cells, regulatory T-cells, and tolerogenic dendritic cells) in order to modulate recipient immune response and to increase the acceptance and long-term survival of islet allografts (58). Notably, recent clinical trials have shown achievement of stable mixed hematopoietic chimerism and/or operational tolerance in kidney allograft recipients using nonmyeloablative conditioning and donor hematopoietic stem cell infusion (59).

Emerging multidisciplinary approaches are showing great promise for β-cell replacement therapies in the years to come. The rapidly evolving fields of biomedical engineering and regenerative medicine will be of assistance in developing efficient ways to enhance islet engraftment and survival. Biocompatible devices and three-dimensional, functionalized polymers, in alternative implantation sites, may also provide an optimal microenvironment for cell implants and local delivery of immunomodulatory agents (60). Cotransplantation of islets with adjuvant cells (i.e., mesenchimal and endothelial cells) may contribute to local tissue remodeling, with revascularization and immune protection. Efficient encapsulation techniques that confer immune isolation while providing adequate exchange of nutrients to islet cells may allow long-term survival after transplantation using short-term or lower levels of immunosuppression (systemically or locally) (61). Availability of an unlimited source of transplantable insulin-producing cells is highly desirable to overcome the current inadequate supply of human pancreatic islet cells for transplantation. Experimental data support the great potential of adult and embryonic stem cells to generate islet cells in vitro, and current efforts are focused toward improving efficiency, potency, and safety of these cells (62). Similarly, under appropriate conditions, expansion and/or differentiation of putative pancreatic islet cell precursors (ex vivo or in vivo) as well as the use of cells that share common embryonic origin (liver cells) to β-cells show great applicative potential. Xenogeneic islets (i.e., porcine) remain a viable therapeutic option for the near future, particularly if combined with immune isolation strategies and safe immunotherapy (17).

The lesson learned from recent clinical islet transplantation trials in patients with unstable type 1 diabetes is that primary goals are as follows: 1) the achievement of stable, normalized glycemic control, in 2) the absence of severe hypoglycemic episodes with improvement of quality of life, and 3) the prevention of progressive, chronic diabetes complications. Insulin independence, although desirable, at present should not be considered the main objective of islet transplantation, particularly in light of the sustained positive effects achieved with a “marginal” functional islet mass via the restoration of C-peptide secretion and
the significant reduction of insulin requirements.

The safety of the patient always remains the priority, and any attempt to improve metabolic control via islet transplantation should be indeed achieved using strategies that minimize any potential complications. In particular, overall risks and benefits should be carefully addressed for each islet transplant candidate. Strict inclusion criteria, close clinical monitoring, and prompt management of emerging complications can maximize the benefits of the transplants while minimizing side effects. Additionally, recent data have shown the relevance of the center’s experience in islet cell processing (7) as well as the feasibility and containing the cost of islet transplantation consortia, with centralized cell processing facilities that support remote transplant centers (44).

The field of β-cell replacement therapies has evolved substantially over the last decades, and notwithstanding the limited patient population size of most studies in islet transplantation, the steady progress in this field (regarding metabolic control, diabetes complications, and quality of life) justifies the renewed optimism for the potential of cellular therapies in diabetes (17). As the current limitations of islet transplantation are progressively overcome, the indication for clinical application of these strategies will greatly expand from the current very limited eligibility criteria in controlled clinical research trials to more widely available cellular therapies and regenerative medicine solutions that will eventually be offered as treatment to the majority of patients with insulin-requiring diabetes.

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APPENDIX — For further information including transplant data and annual reports, please refer to the U.S. Department of Health and Human Services (www.hhs.gov), Organ Procurement and Transplantation Network (www.optn.org), Scientific Registry of Transplant Recipients (www.ustransplant.org), Health Resources and Services Administration (www.hrsa.gov), CITR (www.citregistry.org), and CIT Consortium (www.citisletstudy.org).

References
1. Vantyghem M-C, Kerr-Conje T, Arnalte-teen L, Sergent G, Defrance F, Gmyr V, Declercq N, Raverdy V, Vandewalle B, Pigny P, Noel C, Pattou F. Primary graft function, metabolic control, and graft survival after islet transplantation. Diabetes Care 2009;32:1473–1478
2. Ryan EA, Paty BW, Senior PA, Lakey JR, Bigam D, Shapiro AM. β-Score: an assessment of β-cell function after islet transplantation. Diabetes Care 2005;28:343–347
3. Rickels MR, Najj A, Tell KL. Acute insulin responses to glucose and arginine as predictors of β-cell secretory capacity in human islet transplantation. Transplantation 2007;84:1357–1360
4. Baidal D, Faradji RN, Messinger S, Froud T, Monroy K, Ricordi C, Alejandro A. Early metabolic markers of islet allograft dysfunction. Transplantation 2009;87:689–697
5. Ryan EA, Paty BW, Senior PA, Bigam D, Alaffahidi E, Kneteman NM, Lakey JR, Shapiro AM. Five-year follow-up after clinical islet transplantation. Diabetes 2005;54:2060–2069
6. Froud T, Ricordi C, Baidal DA, Hafiz MM, Ponte G, Cure P, Pileggi A, Poglioli R, Ichii H, Khan A, Ferreina JV, Pugliese A, Esquenazi VV, Kenyon NS, Alejandro R. Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: Miami experience. Am J Transplant 2005;5:2037–2046
7. Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, Secchi A, Brendel MD, Berney T, Brennan DC, Caglhero E, Alejandro R, Ryan EA, DiMercurio B, Morel P, Polonsky KS, Rems JA, Bretzel RG, Bertuzzi F, Froud T, Kandaswamy R, Sutherland DE, Eisenbarth G, Segal M, Preiksaitis J, Korbutt GS, Barton FB, Viviano L, Sefy-Margolis V, Bluestone J, Lakey JR. International trial of the Edmonton protocol for islet transplantation. N Engl J Med 2006;355:1318–1330
8. Cure P, Pileggi A, Froud T, Messinger S, Faradji RN, Baidal DA, Cardani R, Curry A, Poglioli R, Pugliese A, Betancourt A, Esquenazi V, Ciancio G, Selvaggi G, Burke GW 3rd, Ricordi C, Alejandro R. Improved metabolic control and quality of life in seven patients with type 1 diabetes following islet after kidney transplantation. Transplantation 2008;85:801–812
9. Bellin MD, Kandaswamy R, Parkey J, Zhang HJ, Liu B, Ihm SH, Ansite JD, Ryan EA, Wilson J, Bansal-Pakala P, Balamurugan AN, Papas K, Sutherland DE, Moran A, Hering BJ. Prolonged insulin independence after islet allotransplants in recipients with type 1 diabetes. Am J Transplant 2008;8:2463–2470
10. Mineo D, Sageshima J, Burke GW, Ricordi C. Minimization and withdrawal of steroids in pancreas and islet transplantation. Transpl Int 2009;22:20–37
11. Hering BJ, Parkey J, Kandaswamy R, Jevne R, Snead D, Lervik B, Harmon JV, Tanaka T, YoneKawa Y, Matsumoto S, Balamurugan AN, Papas KK, Pakala P,
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Sutherland DER. Analysis of long-term islet allograft function in recipients with type 1 diabetes giving deleterious T-cell antibodies for induction immunosuppression [Abstract]. Xenotransplantation 2007;14:398.A205.3

12. Gruessner RW, Sutherland DE, Kanda-swamy R, Gruessner AC. Over 500 solitary pancreas transplants in nonuremic patients with brittle diabetes mellitus. Transplantation 2008;85:42–47

13. American Diabetes Association. Standards of medical care in diabetes—2009 (Position Statement). Diabetes Care 2009;32: S1–S61

14. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329: 977–986

15. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 1997;46:271–286

16. Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA 2003;290:2817–2823

17. Ricordi C. Islet transplantation: a brave new world. Diabetes 2003;52:1595–1603

18. Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warmock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000; 343:230–238

19. Hering BJ, Kandaswamy R, Harmon JV, Ansite JD, Clemmings SM, Sakai T, Paraskevas S, Eckman PM, Sageshima J, Nakano M, Sawada T, Matsumoto I, Zhang HJ, Sutherland DE, Bluestone JA. Transplantation of cultured islets from two-layer preserved pancreases in type 1 diabetes with anti-CD3 antibody. Am J Transplant 2004;4:390–401

20. Hering BJ, Kandaswamy R, Ansite JD, Eckman PM, Nakano M, Sawada T, Ma-tsumoto I, Ihm SH, Zhang HJ, Parkery J, Patient DW, Sutherland DE. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. JAMA 2005;293:830–835

21. Tan J, Yang S, Cai J, Guo J, Huang L, Wu Z, Chen J, Luo L. Simultaneous islet and kidney transplantation in seven patients with type 1 diabetes and end-stage renal disease using a glucocorticoid-free immunosuppressive regimen with alemtuzumab induction. Diabetes 2008;57:2666–2671

22. Alejandro R, Barton FB, Hering BJ, Wease S. 2008 Update from the Collaborative Islet Transplant Registry. Transplantation 2008;86:1783–1788

23. Tharavani T, Betancourt A, Messinger S, Cure P, Leitao CB, Baidal DA, Froud T, Ricordi C, Alejandro R. Improved long-term health-related quality of life after islet transplantation. Transplantation 2008; 86:1161–1167

24. Paty BW, Ryan EA, Shapiro AM, Lakey JR, Robertson RP. Intrahepatic islet transplantation in type 1 diabetic patients does not restore hypoglycemic hormonal counterregulation or symptom recognition after insulin independence. Diabetes 2002;51:3428–3434

25. Rickels MR, Schutta MH, Mueller R, Markmann JF, Barker CF, Naji A, Teff KL. Islet cell hormonal responses to hypogly-cemia after human islet transplantation for type 1 diabetes. Diabetes 2005;54: 3205–3211

26. Rickels MR, Schutta MH, Mueller R, Kapoor S, Markmann JF, Naji A, Teff KL. Glycemic thresholds for activation of counterregulatory hormone and symptomatic responses in islet transplant recipients. J Clin Endocrinol Metab 2007:92: 873–879

27. Leitão CB, Tharavani T, Cure P, Pileggi A, Baidal DA, Ricordi C, Alejandro R. Restoration of hypoglycemia awareness after islet transplantation. Diabetes Care 2008; 31:2113–2115

28. Poggioli R, Poggioli A, Messinger S, Alejandro A, Ichii H, Baidal DA, Khan A, Ricordi C, Goss JA, Alejandro R. Toward maximizing the success rates of human islet isolation: influence of donor and isolation factors. Cell Transplantation 2007:16:595–607

29. Stegall MD, Dean PG, Sung R, Guidinger MK, McBride MA, Sommers C, Basadonna G, Stock PG, Leichtman AB. The rationale for the newly deceased donor pancreas allocation schema. Transplantation 2007;83:1156–1161

30. Porretti PM, Yeh H, Frank A, Deng S, Kim JJ, Barker CF, Markmann JF. Availability of suitable islet donors in the United States. Transplantation 2007;84:280–282

31. Markmann JF, Kaufman DB, Ricordi C, Schwab PM, Stock PG. Financial issues constraining the use of pancreata recovered for islet transplantation: a white pa-per. American Transplantation 2008;15:1388–1392

32. Daneman D. Type 1 diabetes. Lancet 2006;367:847–858

33. Del Carro U, Fiorina P, Amadio S, de Toni Franceschini L, Petrilli A, Menini S, Boneschi FM, Ferrari S, Pugliese G, Maffi P, Comi G, Scelci A. Evaluation of polynu-tropathy markers in type 1 diabetic kidney transplant patients and effects of islet transplantation: neurophysiological and skin biopsy longitudinal analysis. Diabetes Care 2007;30:3063–3069

34. Fiorina P, Folli F, Bertuzzi F, Maffi P, Finzi G, Venturini M, Socci C, Davalli A, Orsenigo E, Monti L, Falqui L, Uccella S, La Rosa S, Usellini L, Properzi G, Di Carlo V, Del Maschio A, Capella C, Secchi A. Long-term beneficial effect of islet transplantation on diabetic macro/microangiopathy in type 1 diabetic kidney-transplanted patients. Diabetes Care 2003; 26:1129–1136

35. Fiorina P, Gremizzi C, Maffi P, Caldara R, Tavano D, Monti L, Socci C, Folli F, Fazio F, Astorri E, Del Maschio A, Secchi A. Islet transplantation is associated with an improvement of cardiovascular function in type 1 diabetic kidney transplant patients. Diabetes Care 2005;28:1358–1365

36. Fiorina P, Venturini M, Folli F, Losio C, Maffi P, Placidi C, La Rosa S, Orsenigo E, Socci C, Capella C, Del Maschio A, Secchi A. Natural history of kidney graft survival, hypertrophy, and vascular function in end-stage renal disease type 1 diabetic kidney-transplanted patients: beneficial impact of pancreas and successful islet co-transplantation. Diabetes Care 2005;28: 1303–1310

37. Bunnappadisth S, Cho YW, Cecka JM, Wilkinson A, Danovitch GM. Kidney allograft and patient survival in type 1 diabetic recipients of cadaveric kidney alone versus simultaneous pancreas-kidney transplants: a multivariate analysis of the UNOS database. J Am Soc Nephrol 2003; 14:208–213

38. Hansen A, Johansson B, Wahren J, von Bibra F. C-peptide exerts beneficial effects on myocardial blood flow and function in patients with type 1 diabetes. Diabetes 2002;51:3077–3082

39. Hafiz MM, Faradji RN, Froud T, Pileggi A, Baidal DA, Cure P, Ponte G, Poggioli R, Cornejo A, Messinger S, Ricordi C, Alejandro R. Immunosuppression and procedure-related complications in 26 patients with type 1 diabetes mellitus receiving allogeneic islet cell transplantation. Transplantation 2005;80:1718–1728

40. Senior PA, Zeman M, Paty BW, Ryan EA, Shapiro AM. Changes in renal function after clinical islet transplantation: fouryear observational study. Am J Transplant 2007;7:91–98

41. Maffi P, Bertuzzi F, De Taddeo F, Magistretti P, Nano R, Fiorina P, Camuo A, Pozzi P, Socci C, Venturini M, del Maschio A. Simultaneous islet transplantation after islet transplant alone in type 1 diabetes: impact of immunosuppressive therapy on progression of diabetic nephropathy. Diabetes Care 2007;30:1150–1155

42. Warmack GL, Thompson DM, Meloche RM, Shapiro RJ, Aze K, Keown P, Johnson JD, Verchere CB, Partovi N, Begg IS, Fung M, Kozak SE, Tong SO, Alghofaili KM, Harris C. A multi-year analysis of islet transplantation compared with intensive medical therapy on progression of complications in type 1 diabetes. Transplantation 2008;86:1762–1766

43. Leitão CB, Cure P, Messinger S, Pileggi A,
Lenz O, Froud T, Faradji RN, Selvaggi G, Kupin W, Ricordi C, Alejandro R. Stable renal function after islet transplantation: importance of patient selection and aggressive clinical management. Transplantation 2009;87:681–688

44. Pileggi A, Cobianchi L, Inverardi L, Ricordi C. Overcoming the challenges now limiting islet transplantation: a sequential, integrated approach. Ann N Y Acad Sci 2006;1079:383–398

45. Nir T, Melton DA, Dor Y. Recovery from diabetes in mice by beta cell regeneration. J Clin Invest 2007;117:2553–2561

46. Mohanakumar T, Narayanan K, Desai N, Baidal DA, Cure P, Ponte GG, Mineo D, Faradji RN, Froud T, Pileggi A, Messinger S, Baidal DA, Ponte GM, Cure PE, Monroy K, Mendez A, Selvaggi G, Ricordi C, Alejandro R. The use of exenatide in islet transplant recipients with chronic allograft dysfunction: safety, efficacy, and metabolic effects. Transplantation 2008;86:36–45

47. Cardani R, Pileggi A, Gomez C, Baidal DA, Ponte GG, Mineo D, Faradji RN, Froud T, Ciancio G, Esquenazi V, Burke GW 3rd, Selvaggi G, Miller J, Kenyon NS, Alejandro R. Allosensitization of islet allograft recipients. Transplantation 2007;84:1413–1427

48. Campbell PM, Salam A, Lohan J, Black M, Benison P, Benshoff N, Ramachandran S, Shenoy S, Jendrisak M, Susskind BM, Brennan DC, Fernandez LA, Odorico JS, Polonsky KS. A significant role for histocompatibility in human islet transplantation. Transplantation 2008;86:1658–1665

49. Sykes M. Hematopoietic cell transplantation for tolerance induction: animal models to clinical trials. Transplantation 2009;87:309–316

50. Ricordi C, Edlund H. Toward a renewable source of pancreatic beta-cells. Nat Biotechnol 2008;26:397–398

51. Litu C, Noorchashm H, Sutter JA, Naji M, Prak EL, Boyer J, Green T, Rickels MR, Tomaszewski JE, Koehlerlein B, Wang Z, Paessler ME, Velidedeoglu E, Rostami SY, Yu M, Barker CF, Naji A. B lymphocyte-directed immunotherapy promotes long-term islet allograft survival in nonhuman primates. Nat Med 2007;13:1295–1298

52. Mineo D, Ricordi C, Xu X, Pileggi A, Garcia-Morales R, Khan A, Baidal DA, Han D, Monroy K, Miller J, Pugliese A, Froud T, Inverardi L, Kenyon NS, Alejandro R. Combined islet and hematopoietic stem cell allotransplantation: a clinical pilot trial to induce chimerism and graft tolerance. Am J Transplant 2008;8:1262–1274

53. Pileggi A, Molano RD, Sanabria NY, Tejada T, Gonzalez-Quintana J, Ichii H, Inverardi L, Ricordi C, Pastor RL. Inhibition of c-Jun N terminal kinase (JNK) improves functional beta cell mass in human islets and leads to AKT and glycogen synthase kinase-3 (GSK-3) phosphorylation. Diabetologia 2008;51:298–308

54. The caspase selective inhibitor EP1013 augments human islet graft function and longevity in marginal mass islet transplantation in mice. Diabetes 2008;57:1556–1566

55. Froud T, Baidal DA, Faradji R, Cure P, Mineo D, Selvaggi G, Kenyon NS, Ricordi C, Alejandro R. Islet transplantation with alemutzumab induction and calcineurin-free maintenance immunosuppression results in improved short- and long-term outcomes. Transplantation 2008;86:1695–1701

56. Yu M, Barker CF, Naji A. B lymphocyte-directed immunotherapy promotes long-term islet allograft survival in nonhuman primates. Nat Med 2007;13:1295–1298

57. Ricordi C, Strom TB. Clinical islet transplantation: advances and immunological challenges. Nat Rev Immunol 2004;4:259–268

58. Mineo D, Ricordi C, Xu X, Baidal DA, Ponte GG, Esquenazi V, Burke GW 3rd, Selvaggi G, Miller J, Kenyon NS, Alejandro R. Allosensitization of islet allograft recipients. Transplantation 2007;84:1413–1427

59. Pileggi A, Molano RD, Sanabria NY, Tejada T, Gonzalez-Quintana J, Ichii H, Inverardi L, Ricordi C, Pastor RL. Inhibition of c-Jun N terminal kinase (JNK) improves functional beta cell mass in human islets and leads to AKT and glycogen synthase kinase-3 (GSK-3) phosphorylation. Diabetologia 2008;51:298–308

60. Baidal DA, Cure P, Ponte GM, Monroy K, Mineo D, Baidal DA, Cure PE, Mendez A, Selvaggi G, Ricordi C, Alejandro R. Long-term insulin independence and improvement in insulin secretion after supplemental islet infusion under exenatide and etanercept. Transplantation 2008;86:1658–1665

61. Fornoni A, Pileggi A, Sanabria NY, Tejada T, Gonzalez-Quintana J, Ichii H, Inverardi L, Ricordi C, Pastor RL. Inhibition of c-Jun N terminal kinase (JNK) improves functional beta cell mass in human islets and leads to AKT and glycogen synthase kinase-3 (GSK-3) phosphorylation. Diabetologia 2008;51:298–308

62. Froud T, Baidal DA, Faradji R, Cure P, Mineo D, Selvaggi G, Kenyon NS, Ricordi C, Alejandro R. Islet transplantation with alemutzumab induction and calcineurin-free maintenance immunosuppression results in improved short- and long-term outcomes. Transplantation 2008;86:1695–1701

63. Liu C, Noorchashm H, Sutter JA, Naji M, Prak EL, Boyer J, Green T, Rickels MR, Tomaszewski JE, Koehlerlein B, Wang Z, Paessler ME, Velidedeoglu E, Rostami SY, Yu M, Barker CF, Naji A. B lymphocyte-directed immunotherapy promotes long-term islet allograft survival in nonhuman primates. Nat Med 2007;13:1295–1298

64. Ricordi C, Strom TB. Clinical islet transplantation: advances and immunological challenges. Nat Rev Immunol 2004;4:259–268

65. Mineo D, Ricordi C, Xu X, Pileggi A, Garcia-Morales R, Khan A, Baidal DA, Han D, Monroy K, Miller J, Pugliese A, Froud T, Inverardi L, Kenyon NS, Alejandro R. Combined islet and hematopoietic stem cell allotransplantation: a clinical pilot trial to induce chimerism and graft tolerance. Am J Transplant 2008;8:1262–1274

66. Sykes M. Hematopoietic cell transplantation for tolerance induction: animal models to clinical trials. Transplantation 2009;87:309–316

67. Pileggi A, Molano RD, Ricordi C, Zahr F, Collins J, Valdes R, Inverardi L. Reversal of diabetes by pancreatic islet transplantation into a subcutaneous, neovascularized device. Transplantation 2006;81:1318–1324

68. Calafiore R, Basta G, Luca G, Lemmi A, Montanucci MP, Calabrese G, Raciarcich L, Mancuso F, Brunetti P. Microencapsulated pancreatic islet allografts into non-immunosuppressed patients with type 1 diabetes: first two cases. Diabetes Care 2006;29:137–138