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Islet Cell Transplantation for Patients with Unstable or Uncontrollable Diabetes Mellitus: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

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Abbreviations

AMSTAR 2	A Measurement Tool to Assess Systematic Reviews 2
CSII	continuous subcutaneous insulin infusion
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	glycated hemoglobin A1c
ICER	incremental cost-effectiveness ratio
NRS	non-randomized study
QALY	quality-adjusted life year
RCT	randomized controlled trial
SR	systematic review

Context and Policy Issues

Type 1 diabetes is a chronic autoimmune disease characterized by the destruction of pancreatic beta cells which leads to an insulin deficiency.[1] The onset of type 1 diabetes mostly occurs before 25 years of age, but can also occur later in life.[1] In 2015, 3.4 million Canadians were living with diabetes, of which an estimated 9% of adult patients and most pediatric patients are classified as type 1. Of this cohort, 0.3% of patients suffer from labile diabetes (also referred to as brittle or unstable diabetes and meaning hard to control) and may experience frequent episodes of hyperglycemia and hypoglycemia, diabetic ketoacidosis, and hypoglycemic unawareness.[2] The lability of these patients' blood glucose levels leads to a decreased quality of life and may reduce life expectancy.[2]

Type 1 diabetes is generally treated with insulin replacement therapy in the form of multiple daily injections.[1] However, one alternative to insulin therapy, which may be beneficial to patients with labile diabetes, involves restoring endogenous insulin production via islet cell transplantation.[3] Islet cell transplantation involves the infusion of purified islet cells from a deceased donor pancreas into the liver through the portal vein.[3] As such, islet cell transplantation recipients require life-long treatment with immunosuppressive agents.[3] With the introduction of ever improving, steroid free immunosuppression regimens (the first of which was the Edmonton Protocol in the year 2000), islet cell transplantation has become an increasingly feasible treatment option for patients with labile diabetes.[2]

In patients with type 1 diabetes, islet cell transplantation may result in glucose stability (i.e., a reduction or elimination of hypoglycemia), improvement in glycated hemoglobin A1c (HbA1c), insulin independence, and may stabilize or improve microvascular complications (retinopathy and neuropathy) of diabetes.[3] However, as a result of the small number of specialized transplantation centers and donor pancreases, the availability of treatment with islet cell transplantations for patients with type 1 diabetes has been limited.[3]

A CADTH report[4] published in 2014 reviewed the clinical effectiveness, cost-effectiveness, and evidence-based guidelines regarding islet cell transplantation in patients with unstable diabetes. The report concluded that there was limited evidence to suggest that islet transplantation was effective in improving clinical outcomes in patients with unstable type 1 diabetes.[4] Another CADTH report,[5] which examined islet cell transplantation relative to different interventions, was published in March 2020 and provided a reference list of studies and evidence-based guidelines published since the end of the aforementioned report's literature search. This report aims to provide a summary and critical appraisal of the evidence regarding the clinical effectiveness, cost-effectiveness, and evidence-based guidelines regarding the use of islet cell transplantation in patients with unstable type I diabetes mellitus which was identified in the previous CADTH Reference List report.[5]

Research Questions

1. What is the clinical effectiveness of islet cell transplantation in patients with unstable type I diabetes mellitus?
2. What is the cost-effectiveness of islet cell transplantation in patients with unstable type I diabetes mellitus?
3. What are the evidence-based guidelines regarding the use of islet cell transplantation in patients with unstable type I diabetes mellitus?

Key Findings

One systematic review, one randomized controlled trial, and five non-randomized studies were identified regarding the clinical effectiveness of islet cell transplantation compared to insulin therapy in patients with unstable type 1 diabetes. Overall, compared to insulin therapy, islet cell transplantation was associated with better glycemic control, quality of life, and some secondary complications of diabetes including macrovascular and microvascular complications. However, the results of these studies should be interpreted with caution as numerous methodological limitations were identified. One relevant economic evaluation was identified which compared the cost-effectiveness of islet cell transplantation to intensive insulin therapy in a theoretical cohort of patients with unstable type 1 diabetes. Islet cell transplantation was not cost-effective. One evidence-based guideline developed by Diabetes Canada was identified that states that patients with unstable type 1 diabetes who have preserved renal function or who have had a successful kidney transplant may be considered for islet cell transplantation (low quality evidence; weak recommendation).

Methods

Literature Search Methods

This report makes use of a literature search conducted for a previous CADTH report.[5] The limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were islet cell transplantation and type 1 diabetes. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and February 25, 2020. Internet links were provided, where available.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with unstable, uncontrollable, or unawareness type I diabetes mellitus
Intervention	Islet cell transplantation
Comparators	Standard treatment with insulin and insulin related devices (i.e., injection, insulin pumps)
Outcomes	Q1: Clinical effectiveness (e.g., blood glucose, HbA1c, regression of type I diabetes, use of insulin) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-year) Q3: Recommendations regarding the use of islet cell transplantation for patients with unstable or uncontrolled type I diabetes
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

HbA1c = glycated hemoglobin A1c.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic review (SR) was critically appraised by one reviewer using A Measurement Tool to Assess Systematic Reviews 2[6] (AMSTAR 2), primary clinical studies were critically appraised using the Downs and Black Checklist,[7] the economic evaluation was assessed using the Drummond Checklist,[8] and the evidence-based guideline was assessed with the Appraisal of Guidelines for Research and Evaluation II[9] (AGREE II) instrument. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 359 citations were identified in the literature search. Following screening of titles and abstracts, 351 citations were excluded and eight potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, four publications were excluded for various reasons, and nine publications met the inclusion criteria and were included in this report. These comprised one SR,[2] one randomized controlled trial (RCT),[10] five non-randomized studies (NRSs),[11-15] one economic evaluation,[16] and one evidence-based guideline.[3] Appendix 1 presents the PRISMA[17] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of the included publications are provided in Appendix 2.

Study Design

One SR,[2] published in 2015, searched two databases for studies published from January 1, 2003 to November 27, 2014. The SR used a two-step process to identify relevant literature.[2] First, a search for systematic reviews and health technology assessments was conducted, and a recent and methodologically sound health technology assessment was identified.[2] Second, a search for primary studies (from December 2010 to November 27, 2014 with alerts until March 23, 2014) was conducted to update the chosen health technology assessment.[2] The SR assessed the quality of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group.[2] The quality of the evidence for each outcome was assigned a GRADE: High (the true effect lies close to the estimate of the effect), Moderate (the true effect is most likely close, but may also be substantially different than the estimate of the effect), Low (the true effect may be substantially different than the estimate of the effect), or Very Low (the true effect is likely to be substantially different than the estimate of the effect).[2] The GRADE assignment first considered study design (randomized controlled trials were high quality; observational studies were low quality).[2] Limitations that lowered the quality of evidence (i.e., risk of bias, inconsistency, indirectness, imprecision, and publication bias) and strengths that raised the quality of evidence (e.g., a large magnitude of effect) were also considered for the final GRADE assignment.[2] The SR had inclusion criteria that were broader in scope than the criteria for this report as different comparators (e.g., pancreas transplantation) were also included.[2] Thus, the SR contained seven observational comparative studies and 25 case series relevant to this report.[2] Only the characteristics and results of the subset of relevant studies will be described in this report.

Six primary clinical studies relevant to this report were identified, including one RCT and five NRSs. The RCT[10] was a phase 3, open-label, multicenter, two-arm trial published in 2018. The five NRSs were a prospective, parallel-arm, cohort study (with the two arms combined for a comparison against baseline) published in 2019;[11] a before-and-after study published in 2018;[12] a study published in 2017 which used data from two previous single arm studies;[13] a phase 3 prospective, open-label, single arm study published in 2016;[14] and a study published in 2015 which used data from two single arm trials.[15]

The economic evaluation,[16] published in 2016, was a Markov model based, cost-utility analysis from the perspective of a provincial health care payer (Alberta Health Services). The evaluation used a lifetime time horizon (62.5 years) and obtained their clinical and cost inputs from four clinical studies, the University of Alberta Hospital, and expert opinion.[16] The main assumptions made in the analysis included the proportion of patients with partial and full graft function per transplant cycle, the reduction in diabetes-related complications over the model time horizon, the reduction of life expectancy in patients treated with intensive insulin therapy, and the proportion of patients experiencing complications secondary to the immunosuppressive regimen.[16]

One evidence-based guideline,[3] published in 2018, was developed by Diabetes Canada and was informed by a SR of the literature. The Diabetes Canada guideline assigned a level of evidence (highest being 1a and lowest being 4) and a grade (highest being A and lowest being D) a to each recommendation.[3] Diabetes Canada utilizes a standardized methodology for each of their guidelines; as such, specific details regarding the methodology used to develop the guideline were not provided.[3] Additional details regarding the level of evidence and grade of recommendation ratings are provided in Appendix 2.

Country of Origin

The authors of the SR[2] were based in Canada. The relevant primary studies included in the SR were conducted in Canada, the United States, Italy, France, Switzerland, Belgium, Sweden and Australia.[2] The RCT[10] was conducted in France and Switzerland whereas the five NRSs were conducted in France,[11,15] the United States[12,14], Switzerland,[15] and Australia.[13] The economic evaluation[16] was conducted in Canada. The Diabetes Canada guideline[3] was developed for Canada.

Patient Population

The SR included adult (aged 18 years or older) patients with type 1 diabetes mellitus with or without kidney disease.[2] The sample size in the relevant primary studies ranged from 20 to 75 patients for comparative observational studies and from 10 to 99 patients for case series studies.[2]

The RCT[10] was conducted at 15 university hospitals and included 50 patients living with type 1 diabetes for a minimum of 5 years. These patients had a history of severe glycemic lability associated with at least two severe hypoglycemia events per year, had a severe impairment in quality of life due to the hypoglycemic events, and had hypoglycemia unawareness.[10]

The five NRSs included adult patients with type 1 diabetes and a history of hypoglycemic events.[11-15] The sample size in the five NRSs ranged from 10[13] to 48[12,14] patients. They were conducted at hospitals or used data from studies conducted at hospitals.[11-15] The median baseline number of severe hypoglycemia events varied by study and ranged from 2[11] to 8[13] per year.[11-15]

The patient population in the economic evaluation was a hypothetical cohort of patients with unstable type 1 diabetes that met the transplantation inclusion criteria of the University of Alberta Hospital.[16] The transplantation criteria used were unclear.

The target population for the Diabetes Canada guideline is Canadians living with diabetes.[3] Its intended users are healthcare professionals involved in the management of patients with diabetes and Canadians living with diabetes.[3]

Interventions and Comparators

The relevant primary studies in the SR compared all types of islet transplantation (i.e., islet transplantation alone, islet-after-kidney transplantation and simultaneous islet-kidney transplantation) to intensive insulin therapy, a waiting list or to baseline (i.e., before-and-after studies).[2] The types of insulin or the regimens used by patients were not provided.[2]

The RCT[10] first compared islet cell transplantation to a flexible insulin therapy regimen (types of insulin and regimens not provided, but insulin doses were adjusted every 3 months to achieve an HbA1c <7% without severe hypoglycemia). At 6 months post-randomization, the insulin therapy group was registered on the transplantation list and received an islet cell transplantation as soon as a compatible preparation was available.[10] At 12 months after the first islet cell infusion (in both trial arms), the full cohort was compared to baseline.[10] Again, the types of insulin and regimens used by the patients at baseline were not provided.

Four of the NRSs[11,12,14,15] compared islet cell transplantation to baseline (types of insulin and regimens patients used at baseline were not provided). A fifth NRS[13] compared islet

cell transplantation to continuous subcutaneous insulin infusion (CSII). Patients used multiple daily injections at baseline and were switched to CSII for at least 3 months prior to undergoing islet cell transplantation.[13]

The economic evaluation[16] compared islet cell transplantation to intensive insulin therapy (manual or device-based injections).

The Diabetes Canada guideline[3] considered the interventions of islet cell allotransplantation, islet cell autotransplantation after pancreatectomy and pancreas transplantation. The intervention of interest for this report was islet cell allotransplantation.

Outcomes

The outcomes considered in the SR[2] were glycemic control (i.e., HbA1c, hypoglycemia events/unawareness, graft loss/insulin independence, and reduction in insulin dose requirements), secondary complications of diabetes (i.e., cardiovascular disease and risk factors, nephropathy, retinopathy and neuropathy), health-related quality of life (both generic and diabetes specific questionnaires), and adverse events of the procedure and maintenance of islet cell transplantation.

In the RCT,[10] outcomes were measured 6 months after the first infusion in the immediate transplantation group and compared to a group who continued 6 months of insulin therapy. The primary outcome was the proportion of participants with a modified β-score of 6 or higher. The modified β-score is based on the following variables: fasting glucose, fasting or stimulated C-peptide, HbA1c, and absence of insulin or oral hypoglycemic drug use.[10] Up to two points are rewarded for each variable; the score can range from 0 (no graft function) to 8 (optimal graft function).[10] Secondary outcomes, were glycemic control (i.e., HbA1c, fasting blood glucose level, proportion of participants with an HbA1c <7% without severe hypoglycemia, number of severe hypoglycemia events per year, proportion of participants free from severe hypoglycemia, number of non-severe hypoglycemia events per year, and insulin requirements), and quality of life (Short Form 36 Health Survey and the Diabetes Quality of Life questionnaire).[10] Outcomes assessed at 12 months after the first islet cell infusion in the full cohort were the previously listed glycemic control outcomes and the proportion of participants achieving insulin independence and the median Clarke Score.[10] Insulin independence was defined as the ability to maintain an HbA1c <7% and 2-hour post-prandial blood glucose levels <10 mmol/L without exogenous insulin while maintaining a stimulated or fasting plasma C-peptide level of ≥17 nmol/L.[10] The Clarke score consists of questions on hypoglycemia awareness and the presence or absence of symptoms accompanying low blood glucose.[10] The score can range from 0 to 8 where a score of 5 or higher indicates the presence of hypoglycemia unawareness.[10]

Four NRSs reported the effects of islet cell transplantation on various outcomes of glycemic control (i.e., HbA1c,[11,13-15] hypoglycemia events,[11,13-15] insulin requirements,[11,13-15] insulin independence,[11,14,15] various blood glucose measurements via continuous glucose monitoring,[11,13] and fasting blood glucose levels[15]). A fifth NRS[12] reported condition-specific health-related quality of life via the Diabetes Distress Scale and the Hypoglycemic Fear Survey and functional health status and health utility via the Short Form 36 Health Survey and EuroQoL 5 Dimensions.

The economic evaluation[16] estimated the incremental cost-effectiveness ratios (ICERs) for islet cell transplantation compared to intensive insulin therapy.

The Diabetes Canada guideline[3] included one recommendation relevant to this report. The guideline development group considered the outcomes of reduction or elimination of hypoglycemia, improvements in HbA1c, and the proportion of patients attaining insulin independence, when formulating the recommendation.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

The included SR had several strengths including a clearly defined objective and clearly described eligibility criteria for the included population, interventions, and outcomes.[2] A comprehensive literature search was performed and the search strategies for the databases were reported and appropriate.[2] A list of included studies was provided and the studies characteristics were well described.[2] The authors appraised the studies for quality and assigned a GRADE quality score to each outcome of interest.[2] The authors also described the heterogeneity across included studies and the decision not to conduct a meta-analysis was justified.[2]

However, the SR was appraised to be of critically low quality using the AMSTAR 2[6] tool because of the numerous weaknesses identified. An *a priori* protocol was not reported, the eligible comparators were unclear and, although reasons for the exclusion of studies were provided, a list of the excluded studies was not provided (so it was unclear which publications may have been omitted). Furthermore, study screening and selection were done by a single reviewer and it was unclear how data extraction was completed.[2] Although the authors appraised the studies for quality, they did not consider the risk of bias for individual studies when interpreting and discussing results. Lastly, the authors disclosed that they had no conflicts of interest related to this review, however, the funding sources of the primary studies were not reported.[2] Thus, the potential impact of funding organizations was unclear.

Randomized Controlled Trial

The RCT[10] had several strengths including a clear research question, relevant population eligibility criteria, and a well-defined intervention which included a description of the immunosuppression regimens. Participants were appropriately randomized and the time period of patient recruitment was provided.[10] The measured outcomes were clearly described and the statistical tests used to assess the main outcomes were described and appropriate.[10] Furthermore, estimates of random variability in the main outcomes were provided.[10] The prespecified sample size was met as 50 patients were included in the trial compared to the calculated 32 participants needed to yield a 95% power to detect a difference between groups in the primary outcome.[10] Drop-out rates were low (one patient in the intervention group and two in the control group) and only one patient in the control group was lost to follow-up.[10] The trial had an *a priori* protocol and was also registered (NCT01148680).[10] Finally, the authors declared the sources of funding for the trial and reported that they had no conflicts of interest.[10]

The RCT[10] also had numerous limitations. The trial was open label for all participants and investigators.[10] Although the majority of the outcomes were objective in nature, some outcomes, such as quality of life, were subjective and there was the possibility that being aware of the treatment assignment may have influenced the results.[10] Differences in

baseline characteristics of the groups were also present (e.g., fasting blood glucose, units of insulin administered per day) and no statistical testing or descriptions of what would represent clinically meaningful differences were provided.[10] Participants in the comparator group were asked to do at least four capillary glucose tests per day, to practice carbohydrate counting and their insulin doses were adjusted every 3 months by the investigator.[10] However, the intervention in the insulin group was poorly described (i.e., may not have constituted intensive insulin therapy) and compliance with insulin regimens was not provided.[10] Thus, there was the possibility that participant glycemic control and adherence may have been negatively influenced by the fact that they would eventually receive islet cell transplantations. Lastly, although the trial was multicenter, it was conducted in France;[10] the results may not be generalizable to the Canadian setting.

Non-Randomized Studies

The five NRSs[11-15] all had clearly described objectives, patient populations which seemed to be representative of the population of interest, and provided the time periods of patient recruitment. Four NRSs[11,12,14,15] had well defined population eligibility criteria, whereas the NRS by Holmes-Walker et al.[13] had unclear inclusion and exclusion criteria. Specifically, the study included 10 participants whereas the two referenced studies from which patient data were retrieved had a total of 23 participants.[13] Furthermore, four NRSs[11,12,14,15] had well defined interventions and included descriptions of the immunosuppression regimens while the intervention and immunosuppression regimens of one NRS[13] were not specifically detailed, but were reported in referenced studies. The five NRSs[11-15] also had clearly described outcomes and provided estimates of random variability in the main outcomes. Whereas four of the NRSs[11-14] described the statistical tests used to assess the main outcomes, one NRS[15] did not provide the details of the statistical analysis. The two prospective NRSs[11,14] used intention-to-treat analyses and provided characteristics of patients lost to follow-up. However, only one prospective NRS[14] conducted a sample size calculation. Finally, the five NRSs[11-15] all reported their funding sources and declared conflicts of interest.

Various limitations were also uniformly present across the five NRSs. Although the five NRSs[11-15] provided baseline characteristics, including exogenous insulin requirements, it was unclear what types of insulin, insulin regimens, or regimens of blood glucose monitoring were used or how insulin requirements were calculated; therefore, the “insulin therapy” comparison was unclear. Furthermore, patient recruitment in the five NRSs began between 2003 and 2008.[11-15] It is unclear if newer technologies (e.g., hybrid closed loop insulin delivery systems) would have provided the patients better glycemic control. Lastly, the five NRSs were conducted in various countries other than Canada;[11-15] the results may not be generalizable to the Canadian setting.

Economic Evaluation

The economic evaluation[16] included numerous strengths such as a clearly stated research question and justification of the economic importance of the research question. The perspective of the analysis, the form of economic evaluation used, the treatment alternatives being compared, the sources of effectiveness estimates and the primary outcome measures were clearly described.[16] Details of the model used were provided and the choice of model used and the key parameters on which it was based were justified.[16] Furthermore, the time horizon of costs and benefits, the discount rate, the choice of discount rate and the currency and price data were provided.[16] The approach to the sensitivity analysis was provided and the choice of variables for the sensitivity analysis was

justified.[16] Major outcomes were presented in a disaggregated as well as an aggregated form, the answer to the study question was provided and conclusions followed from the data reported and were accompanied by the appropriate caveats.[16] Lastly, funding sources of the evaluation were provided and the authors declared that they had no conflicts of interest.[16]

However, the economic evaluation also had limitations. Although the form of economic evaluation was stated, there was no justification for the use of a clinical-utility analysis to address the research question.[16] Furthermore, details of the designs and results of the effectiveness studies (i.e., clinical inputs) were not provided.[16] Quantities of resource use were not reported separately from their unit costs, methods for the estimation of quantities and unit costs were not described, and details of currency price adjustments for inflation were not provided.[16] Furthermore, the majority of the cost information in the economic evaluation was provided by the University of Alberta Hospital.[16] As such, there is uncertainty whether the calculated costs would apply throughout Canada.

Evidence-Based Guideline

The Diabetes Canada guideline[3] was appraised to be of high quality as only minor limitations were identified. The objective of the guideline and the population to whom the guideline is meant to apply were clearly described.[3] Although there was no health question specifically described, the intent of the authors was easily perceived.[3] The guideline development group included relevant healthcare professionals and patient representatives and clearly defined the target users.[3] The development of the guideline included a systematic search for evidence and clear criteria for selecting the evidence.[3] Furthermore, the strengths and limitations of the evidence were clearly described, there was an explicit link between the supporting evidence and the recommendations, and the risks and benefits of islet cell transplantation were considered in the formulation of recommendations.[3] In terms of editorial independence, the guideline development group declared competing interests transparently and the views of funding bodies do not seem to have influenced the content of the guideline.[3] However, the Diabetes Canada guideline did not describe facilitators and barriers to its application, potential resource implications of implementing recommendations, or monitoring criteria.

Summary of Findings

The overall findings of the included studies are highlighted below and Appendix 4 presents tables with summaries of findings and recommendations.

Clinical Effectiveness of Islet Cell Transplantation

Glycemic Control

The identified SR,[2] RCT,[10] and four NRSs[11,13-15] reported glycemic control outcomes.

The SR[2] reported that in non-uremic patients, islet cell transplantation was associated with better glycemic control compared to patients' baseline prior to transplantation in case series or intensive insulin therapy in observational comparative studies. This was based on 15 studies that reported improved graft loss or insulin independence (high quality evidence), 15 studies that reported improved HbA1c (low quality evidence), 11 studies that reported reductions in insulin dose requirements (low quality evidence), and 9 studies that reported improved hypoglycemia events or unawareness (low quality evidence), from before to after islet cell transplantation.[2] Furthermore, in uremic patients, islet cell transplantation was also

associated with better glycemic control compared to patients' baseline prior to transplantation in case series or intensive insulin therapy in observational comparative studies.[2] This was based on 7 studies that reported improved graft loss or insulin independence (high quality evidence), 8 studies that reported improved HbA1c (very low quality evidence), 8 studies that reported reductions in insulin dose requirements (low quality evidence) and 2 studies that reported improved hypoglycemia events or unawareness (low quality evidence), from before to after islet cell transplantation.[2]

The RCT reported there was a significantly greater proportion of patients with a modified β-score of 6 or higher in those who received islet cell transplantation compared to insulin therapy.[10] Furthermore, compared to insulin therapy, islet cell transplantation significantly improved median HbA1c, the median number of severe hypoglycemia events per year, the median number of non-severe hypoglycemia events per year, and the median insulin dose requirements.[10] However, there was no statistically significant difference in median fasting blood glucose levels.[10] In the full cohort, compared to baseline, islet cell transplantation was associated with a significant increase in the proportion of patients with a modified β-score of 6 or higher and was associated with significant reductions in median HbA1c, the median fasting blood glucose level, the median number of severe hypoglycemia events per year, the median number of non-severe hypoglycemia events per year and the median insulin dose requirements.[10] Of the full cohort, 59% of patients achieved insulin independence.[10]

The NRS by Vantyghem et al.[11] reported that following islet cell transplantation there were significant reductions in median HbA1c, median number of severe hypoglycemia events in the previous year, median insulin dose requirements and outcomes measured via continuous glucose monitoring (e.g., median mean glucose, median percentage of time spent below <70 mg/dL) at 1, 5, and 10 years. The NRS by Hering et al.[14] reported that following islet cell transplantation there was a significant increase in the proportion of patients with an HbA1c <7.0% and eradicated severe hypoglycemic events, and significant reductions in median HbA1c, the proportion of participants experiencing at least one severe hypoglycemic event, and median insulin dose requirements at 1 year. The NRS by Lablanche et al.[15] reported that following islet cell transplantation there was a significant increase in the proportion of patients with an HbA1c ≤7% or experiencing a drop in HbA1c of ≥2%, and significant reductions in median HbA1c, mean number of severe hypoglycemic events, and median insulin dose requirements at 5 years follow-up. Similarly, the NRS by Holmes-Walker et al.[13] reported that following islet cell transplantation there were significant reductions in average HbA1c and median hypoglycemic events per person year, and a numerical reduction in the average insulin requirements (statistical analysis not provided). Three of the NRSs[11,14,15] also reported proportions of patients who achieved insulin independence which varied considerably by study and based on the follow-up periods (39% at 5 years and 28% at 10 years[11] 52.1% at 1 year and 42% at 2 years;[14] 45% at 1 year and 31.5% at 5 years in islet after kidney transplant recipients, 37.5% at 1 year and 14% at 5 years in islet cell transplantation alone recipients[15]). Generally, there was a trend in which the proportion of patients with insulin independence decreased over time.

Secondary Complications of Diabetes

The identified SR[2] included evidence on the effect of islet cell transplantation on secondary complications of diabetes. Compared to patients' baseline prior to transplantation in case series or to intensive insulin therapy in observational comparative studies, islet cell transplantation was associated with improvements in secondary complications of diabetes. This was based on 4 studies that reported improved cardiovascular disease (very low quality evidence), 5 studies that reported improved retinopathy (low quality evidence), 6

studies that reported improved nephropathy (very low quality evidence), and 5 studies that reported improved neuropathy (very low quality evidence) in non-uremic patients and 6 studies that reported improved cardiovascular risk (low quality evidence) and 6 studies that reported improved nephropathy (low quality evidence) in uremic patients.[2]

Quality of Life

The identified SR,[2] RCT,[10] and one NRS[12] reported evidence on the effect of islet cell transplantation on the quality of life of patients with labile type 1 diabetes.

The SR contained 12 relevant studies (very low quality evidence) in non-uremic patients and 2 relevant studies (very low quality evidence) in uremic patients which showed health-related quality of life was significantly greater following islet cell transplantation compared to baseline prior to transplantation in case series studies, or compared to continued intensive insulin therapy in observational comparative studies.[2]

The identified RCT found that islet cell transplantation, compared to insulin therapy, significantly improved the median gain in "Satisfaction", "Impact of Diabetes", "Diabetes-Related Worry" and the "Global Score" quality of life dimensions assessed with the Diabetes Quality of Life questionnaire, whereas no statistically significant difference was found in the "Wellbeing" quality of life dimension.[10] The RCT also found that islet cell transplantation, compared to insulin therapy, significantly improved the median gain in "General Health" and "Health Transition" quality of life dimensions assessed with the Short Form 36 Health Survey.[10] However, no statistically significant differences were found in the "Physical Functioning", "Physical Role Limitations", "Bodily Pain", "Vitality", "Social Functioning", "Emotional Role Limitations", "Mental Health", "Physical Component Score" or "Mental Component Score" quality of life dimensions.[10]

The NRS by Foster et al.[12] used four unique questionnaires to determine the effect of islet cell transplantation on quality of life at day 75, 365 and 730 post-transplantation compared to patients' pre-transplantation baseline. Islet cell transplantation was associated with significant improvements in all dimensions of the Diabetes Distress Scale and Hypoglycemia Fear Survey at day 75, 365 and 730 post-transplantation.[12] In terms of the Short Form 36 Health Survey, islet cell transplantation was associated with significant improvements in the "Role Physical Scale", "General Health Scale" and "Vitality Scale" dimensions at day 75, 365 and 730 post-transplantation whereas there were either no significant differences at day 75, 365 or 730 or a significant difference at only one or two of the assessed time periods for the "Physical Component Summary", "Mental Component Summary", "Physical Functioning Scale", "Bodily Pain Scale", "Social Functioning Scale", "Role Emotional Scale", and "Mental Health Scale" dimensions."[12] Finally, in terms of the EuroQoL 5 Dimensions questionnaire, islet cell transplantation was associated with significant improvements in the "Visual Analogue Scale" dimension at day 360 and 730 post-transplantation, but there was no significant difference at any time period for the remaining dimensions ("Health Preference Weight", "Usual Activities", "Anxiety/Depression", "Mobility", "Pain/Discomfort", and "Self-Care").[12]

Adverse Events

The identified SR,[2] RCT,[10] and four NRSs[11,13-15] reported adverse events. The SR contained 21 relevant studies (low quality evidence) in non-uremic patients and 5 relevant studies (low quality evidence) in uremic patients which showed islet cell transplantation was associated with procedure-related and immunosuppression-related adverse events.[2] The RCT reported adverse events in the full cohort of islet cell transplantation recipients as

follows: infections and infestation (43%), gastrointestinal disorders (39%), blood and lymphatic system disorders (35%), procedural complications (20%), and other less prevalent serious adverse events.[10] Of these adverse events, three (15%) infections and infestations and one (4%) blood and lymphatic system disorder occurred during the pre-infusion period while the rest occurred post-transplantation.[10] The NRSs[11,13-15] reported various adverse events related to the transplant procedure, such as bleeding events,[14,15] and adverse events related to immunosuppression such as hematological disorders,[11,13,14] infections,[11,14] and renal dysfunction.[13,14] None of the identified studies reported the statistical significance of these findings.

Cost-Effectiveness of Islet Cell Transplantation

For islet cell transplantation compared to intensive insulin therapy, the ICER was $150,006 per QALY gained which had a 95% probability of being cost-effective at a willingness-to-pay threshold of $196,000, a 13% probability of being cost-effective at a willingness-to-pay threshold of $125,000, and a 0.5% probability of being cost-effective at a willingness-to-pay threshold of $100,000.[16]

Guidelines

The Diabetes Canada guideline[3] states patients with labile type 1 diabetes who have preserved renal function or have had a successful kidney transplant may be considered for islet cell transplantation (Level of Evidence: 3 [evidence from a NRS or SR/MA of NRS]; Grade of Recommendation: C [Best evidence was at Level 3]).

Limitations

There were several limitations to this report, one of which was the quality of evidence identified. Owing to the nature of the intervention, randomizing patients with labile type 1 diabetes to their current therapy (i.e., insulin therapy) may be unethical. As such, most included studies (including those in the SR) were non-randomized and single-arm studies which provided low-quality evidence and had a high risk of bias.

Most studies identified in this report compared islet cell transplantation to intensive insulin therapy or to baseline (which represents some sort of insulin therapy as the population of interest was patients with type 1 diabetes who do not have an alternative to insulin therapy). The identified studies either had unclear descriptions or did not describe the baseline insulin therapy regimens. As such, the effect of islet cell transplantation was compared to unknown types or regimens of insulin. Furthermore, the care of complex patients, such as the population of interest of this report, often involves multidisciplinary and interprofessional teams who provide education or resources regarding nutrition, exercise, and insulin dosing amongst other aspects of treatment.

The identified studies that measured quality of life as an outcome utilized generic or diabetes specific questionnaires. However, these questionnaires may not adequately consider the effect of immunosuppression regimens on quality of life. The medications used for the maintenance of immunosuppression can cause numerous serious side effects[3] Although islet cell transplantation may decrease the consequences of labile diabetes, these effects must be weighed against the need for life-long immunosuppression.

Lastly, the identified studies are at risk of history bias. None of the identified studies took newer diabetes technologies, such as hybrid closed loop insulin delivery systems, into consideration for the treatment of type 1 diabetes. These new and continuously improving

technologies may significantly reduce the burden of labile diabetes making islet cell transplantation an unattractive option.

Conclusions and Implications for Decision or Policy Making

One SR,[2] one RCT,[10] five NRSs,[11-15] and one economic evaluation[16] were identified regarding the clinical effectiveness and cost-effectiveness of islet cell transplantation in patients with unstable diabetes mellitus. Furthermore, one evidence-based guideline[3] was identified regarding the use of islet cell transplantation in patients with unstable diabetes mellitus.

The identified literature reported positive results regarding the clinical effectiveness of islet cell transplantations compared to insulin therapy in patients with labile type 1 diabetes. Overall, the literature suggests that islet cell transplantation may lead to improved glycemic control and quality of life, and reduced secondary complications of diabetes.[2,11-15] However, there were numerous limitations present across the studies, the foremost of which was the poor descriptions of the comparators (i.e., insulin therapy).Furthermore, a trend of decreased insulin independence over time was observed in three NRSs[11,14,15] (statistical analyses not reported) which had long term follow-ups of 2,[14] 5,[15] and 10[11] years, which suggests that the effectiveness of islet cell transplantation may decrease over time. As the patients in the identified studies were often middle-aged (median age 43,[11] 46[15] and 48[14] years) and type 1 diabetes is a life-long, chronic disease, there is also uncertainty regarding the lifetime clinical effectiveness of islet cell transplantations.

Cost-effectiveness was reported in one identified economic evaluation[16] which reported the ICER of islet cell transplantation compared to intensive insulin therapy in a hypothetical cohort of patients with unstable type 1 diabetes. Overall, islet cell transplantation was reported to be not cost-effective.[16]

The Diabetes Canada guideline[3] included one recommendation relevant to this report which was informed by evidence from an NRS or an SR of NRSs. The guideline states that patients with unstable type 1 diabetes who have preserved renal function or who have had a successful kidney transplant may be considered for islet cell transplantation (Level of Evidence: 3; Grade of Recommendation: C).[3]

These findings are largely in agreement with those of the 2014 CADTH report[4] on this topic. In the previous report, there was low quality evidence regarding the clinical effectiveness of islet cell transplantation for patients with unstable type 1 diabetes, in which islet cell transplantation was similarly associated with improved glycemic control, quality of life, and secondary complications.[4] In contrast to the current report, the cost-effectiveness of islet cell transplantation was reported to be undetermined based on the limited evidence identified.[4]

The studies identified in this report suggest islet cell transplantation may be effective in improving the treatment of patients with labile type 2 diabetes. However, the lack of high-quality evidence with long term follow-up suggests the need for well-designed clinical studies to investigate the clinical effectiveness of islet cell transplantation compared to insulin therapy over the lifetime of patients with unstable type 1 diabetes.

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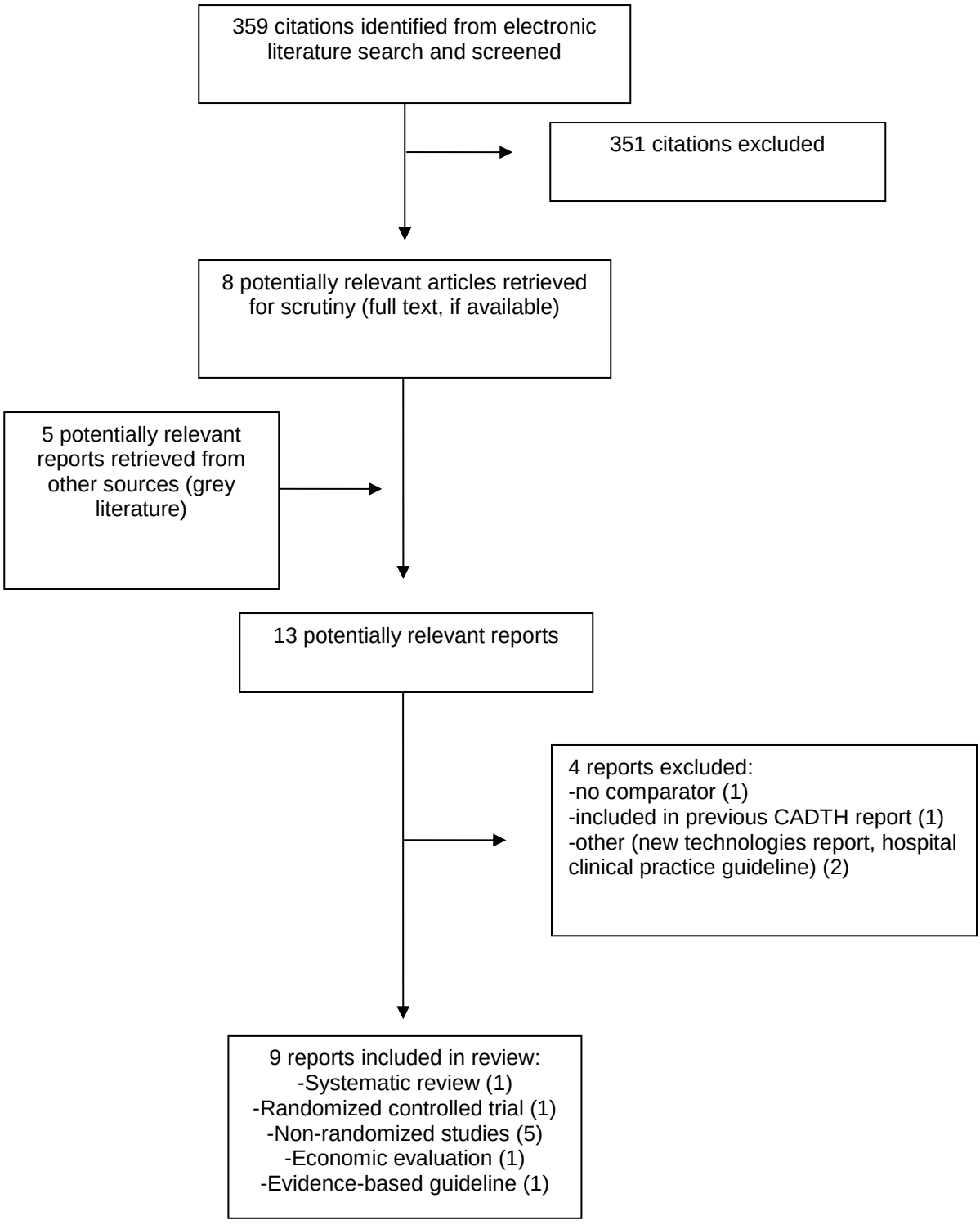
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

First Author, Publication Year, Country, Funding	Study Design, Search Strategy, Number of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparators	Clinical Outcomes, Length of Follow-Up
Health Quality Ontario, 2015[2] **Canada** **Funding:** Not disclosed	**Study design:** Systematic review **Literature search:** Two-step literature search in MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations and EBM Reviews from January 1, 2003 to November 27, 2014. The first step was a search for health technology assessments in which the most recent one with the best methodology was chosen (according to AMSTAR scores) while the second step was a search for primary studies to update the chosen health technology assessment. Reference lists of selected studies were also searched. **Number of studies included:** 17 studies including one health technology assessment representing 2 systematic reviews, 6 observational studies (with 8 publications) and 13 case series (with 20 publications). **Number of studies relevant to this report:** 7 observational comparative studies and 25 case series studies **Quality assessment tool:** AMSTAR tool for health technology assessments and systematic reviews. Assessment of primary studies was conducted using an unnamed tool **Objective:** To determine the clinical effectiveness of islet cell transplantation in patients with type 1 diabetes mellitus (with or without kidney disease)	Patients with type 1 diabetes aged 18 years or older with or without kidney disease	**Intervention:** All types of islet transplantations (islet transplantation alone, islet-after-kidney transplantation, or simultaneous islet-kidney transplantation) **Comparators:** Unclear, however the included studies compared islet transplantation to intensive insulin therapy, a waiting list, baseline (before-and-after studies), or controls such as pancreas transplantation or another islet cell transplantation	• Glycemic control (HbA1c, hypoglycemia events/unawareness, graft loss/insulin independence, reduction in insulin dose requirements) • Secondary complications of diabetes (cardiovascular disease and risk factors, nephropathy, retinopathy, neuropathy) • Adverse events • Health-related quality of life (generic and diabetes specific questionnaires) **Follow-up:** Variable with a minimum of 1 year and the longest being 8 years

AMSTAR = A Measurement Tool to Assess Systematic Reviews; EBM Reviews = Evidence-Based Medicine Reviews; HbA1c = glycated hemoglobin A1c; MEDLINE = Medical Literature Analysis and Retrieval System Online.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country, Funding	Study Design, Setting, Purpose	Population Characteristics	Intervention and Comparator(s)	Relevant Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trial				
Lablanche, 2018[10] **France** **Funding:** Programme Hospitalier de Recherche Clinique grant from the French Government	**Study design:** Phase 3, open-label, two-arm, multicenter, randomized control trial (N= 50). **Setting:** 15 university hospitals in France and three islet preparation units in France (2) and Switzerland (1) **Purpose:** To compare the efficacy of allogenic islet transplantation with insulin therapy for improving metabolic outcomes in patients with type 1 diabetes	Patients with type 1 diabetes diagnosed at least 5 years beforehand and a basal and stimulated C-peptide concentration of <0.1 nmol/mL **Inclusion criteria:** • Presence of severe glycemic lability associated with at least two severe hypoglycemia events per year (defined as one in which the patient required third-party assistance for its correction) • Severe impairment of quality of life related to hypoglycemia • Hypoglycemia unawareness (patient unaware of blood glucose concentrations <3 mmol/L) • Functional kidney graft (GFR >50 mL/min per 1.73m^2, proteinuria <0.5 g per day), poor glycemic control or substantial deterioration in quality of life related to diabetes specifically for patients with type 1 diabetes who received a kidney graft **Exclusion criteria:** • Insulin requirement >0.85 UI/kg/day • BMI >30 kg/m^2 • Pregnancy and women with an intention to conceive or breastfeed • Several diseases: hemostatic disorders, anemia, pre-existing liver disease, gallbladder lithiasis, proliferative retinopathy, nephropathy, macroangiopathy, hypertension, systemic infections including hepatitis B, hepatitis C, and/or HIV • Immunosuppressive treatment with methylprednisolone dose >0.1 mg/kg/day for patients who had received a kidney graft **Number of participants in trial arms (intervention vs. control):** 25 vs. 22	**Intervention:** Immediate islet transplantation. Patients were immediately registered on the transplant list and transplanted as soon as a compatible preparation was available. **Comparator:** Insulin therapy for 6 months followed by registration on the islet transplantation list. Patients were asked to conduct at least 4 capillary glucose tests per day, practice carbohydrate counting and use a flexible insulin therapy regimen. Insulin doses were adjusted every 3 months to achieve an HbA1c <7% without severe hypoglycemia. Pancreases were obtained from brain-dead, multi-organ donors. Patients were scheduled to receive 11,000 islet equivalents/kg in one to three infusions. At 12 months post islet cell infusion in the full cohort (i.e.	**Primary outcome** (measured 6 months after the first infusion in the immediate transplantation group and 6 months after randomization in the insulin group): • Proportion of participants with a modified β-score[a] of 6 or higher **Secondary outcomes** (measured 6 months after the first infusion in the immediate transplantation group and 6 months after randomization in the insulin group): • Median HbA1c • Median fasting blood glucose level • Proportion of participants with an HbA1c <7% without severe hypoglycemia • Median number of severe hypoglycemia events per year • Proportion of participants free from severe hypoglycemia • Median number of non-severe hypoglycemia events per year • Median insulin requirements • Quality of life (Short Form 36 Health Survey and

First Author, Publication Year, Country, Funding	Study Design, Setting, Purpose	Population Characteristics	Intervention and Comparator(s)	Relevant Clinical Outcomes, Length of Follow-Up
		Participant age (intervention vs. control): 52 vs. 51 **Duration of diabetes (intervention vs. control):** 34 years vs. 30 years **Participant average baseline HbA1c (intervention vs. control):** 8.1% vs. 8.1% **Participant average baseline fasting blood glucose (intervention vs. control):** 8.1 mmol/L vs. 9.8 mmol/L **Participant average baseline insulin requirement (intervention vs. control):** 36 units/day vs. 30 units/day **Baseline modified β-score[a] (intervention vs. control):** **0:** 52% vs. 59% **1:** 20% vs. 32% **2:** 24% vs. 9% **3:** 4% vs. 0%	the immediate transplantation group and the transplantation group post 6 month insulin regimen) was compared to baseline	Diabetes Quality of Life questionnaire) **Outcomes assessed at 12 months in the full cohort:** • Proportion of participants with a modified β-score[a] of 6 or higher • Median HbA1c • Median fasting blood glucose level • Proportion of participants with an HbA1c <7% without severe hypoglycemia • Median number of severe hypoglycemia events per year • Proportion of participants free from severe hypoglycemia • Median number of non-severe hypoglycemia events per year • Median insulin requirements • Median Clarke Score[b] • Proportion of participants achieving insulin independence **Follow-up:** At 6 months and 12 months after first islet cell infusion
Non-Randomized Studies				
Vantyghem, 2019[11] **France**	**Study design:** Observational, prospective, parallel-arm, cohort study.	Patients with type 1 diabetes for at least 5 years and a stimulated C-peptide <0.3 ng/mL **Inclusion criteria:**	**Intervention:** Islet cell transplantation consisting of up to three islet	• Median number of severe hypoglycemia events in the previous year

First Author, Publication Year, Country, Funding	Study Design, Setting, Purpose	Population Characteristics	Intervention and Comparator(s)	Relevant Clinical Outcomes, Length of Follow-Up
Funding: French Ministry of Health, Programme Hospitalier de Recherche Clinique 2001, the European Community (Fond Européen de Développement Régional), Conseil Régional du Nord-Pas-de-Calais, Programme d'Investissements D'Avenir Labex European Genomic Institute for Diabetes, Société Francophone du Diabète, Santelys, and Agence de la Biomédecine	The two arms were also combined for a comparison against baseline (N= 28) **Setting:** Participants from two single-arm phase 2 studies conducted at the Lille University Hospital **Purpose:** To evaluate the 10-year outcome of islet transplantation in patients with type 1 diabetes	• Patients with hypoglycemia unawareness and/or documented metabolic lability and an eGFR >60mL/min/1.73m^2 (for non-uremic patients) • Patients with a functioning kidney graft and blood pressure in the normal range (for uremic patients) **Exclusion criteria:** • Aged <18 or >65 years • BMI ≥28 kg/m^2 • Albuminuria >300 mg/24 hours • Unstable arteritis or heart disease • Insulin requirements >1.2 units/kg/day • History of malignancy • Smokers • Desire for pregnancy • Psychiatric disorders • Lack of compliance **Median patient age:** 43 years **Median diabetes duration:** 28 years **Median baseline exogenous insulin requirements:** 0.57 units/kg/day **Median baseline number of severe hypoglycemia events in the previous year:** 2 **Median baseline HbA1c:** 8.15%	infusions within 3 months **Comparator:** Baseline Islets were isolated from pancreases from deceased donors of ABO blood type. Patients received a median of 13,450 islet equivalents/kg.	• Median HbA1c • Median exogenous insulin requirements • Median mean glucose (via continuous glucose monitor) • Median standard deviation of mean glucose (via continuous glucose monitor) • Median time below range (<70 mg/dL) **Follow-up:** 10 years
Foster, 2018[12] **United States** **Funding:** National Institute of Allergy and Infectious Disease, National Institute of Diabetes and Digestive and Kidney Diseases	**Study design:** Before-and-after study using data from a phase 3, prospective, open-label single arm study[14] (N= 48) **Setting:** 8 hospitals in North America **Purpose:** To report the impact of islet transplantation	Patients with type 1 diabetes and a history of severe hypoglycemic events in the previous year Inclusion and exclusion criteria were not reported, but a reference to the original study was provided in the study (see details of Hering et al., 2016[14])	**Intervention:** Islet cell transplantation **Comparator:** Baseline See details of Hering et al., 2016[14]	• Condition specific health-related quality of life via the Diabetes Distress Scale and the Hypoglycemic Fear Survey • Functional health status and health utility via the Short Form 36 Health Survey and EuroQoL 5 Dimensions

First Author, Publication Year, Country, Funding	Study Design, Setting, Purpose	Population Characteristics	Intervention and Comparator(s)	Relevant Clinical Outcomes, Length of Follow-Up
	on health-related quality of life			**Follow-up:** 75, 365 and 730 days post transplantation
Holmes-Walker, 2017[13] **Australia** **Funding:** Juvenile Diabetes Research Foundation, National Health and Research Council Australia	**Study design:** Before-and-after study using data from two previous single arm studies (N= 10) **Setting:** Two hospitals in Australia **Purpose:** To assess the impact of CSII compared to MDI in patients with severe hypoglycemia suitable for islet transplantation and to compare glycemic control with CSII and MDI with that of islet transplantation at 12 months.	Patients with type 1 diabetes mellitus with recurrent severe hypoglycemia (defined as hypoglycemia requiring assistance from a third party to recognize and/or treat) and assessed as suitable for islet transplantation **Average age:** 50.6 years **Average duration of diabetes:** 40.1 years **Average daily insulin requirements:** 0.4 units/kg/day **Median severe hypoglycemia events per person year:** 8 **Average HbA1c:** 8.1%	**Intervention:** Within subject, paired comparison of MDI to CSII and of CSII to 12 months post-islet transplantation	• Average insulin requirements • Average HbA1c • Median HYPOscore[c] • Median hypoglycemic events per person year • Median percentage of time with glucose <4 mmol/L • Median percentage of time with glucose between 4 to 8 mmol/L • Average blood glucose level • Average standard deviation of blood glucose level • Continuous overlapping net glycemic action 4-hour interval **Follow-up:** 12 months post-transplantation
Hering, 2016[14] **United States** **Funding:** National Institute of Allergy and Infectious Diseases, National Institute for Diabetes and Digestive and Kidney Diseases	**Study design:** Phase 3, prospective, open-label, single arm study (N= 48) **Setting:** 8 hospitals in North America **Purpose:** To evaluate the effectiveness and safety of islet transplantations	Patients aged 18 to 65 years with type 1 diabetes for at least 5 years **Inclusion criteria:** • Absent stimulated C-peptide • Impaired awareness of hypoglycemia and/or marked glycemic lability and a history of severe hypoglycemic events in the prior 12 months despite medical care provided by an endocrinologist who asserted that the patient has been compliant with their treatment plan **Exclusion criteria:** • BMI >30kg/m^2	**Intervention:** Islet cell transplantation consisting of up to three islet infusions **Comparator:** Baseline Pancreases were obtained from deceased donors 15 to 65 years of age. The median total dose/kg was 11,972 islet equivalents.	**Primary outcome:** • Proportion of participants with an HbA1c <7.0% with eradication of severe hypoglycemic events **Secondary outcomes:** • Proportion of participants with an HbA1c <6.5% with eradication of severe

First Author, Publication Year, Country, Funding	Study Design, Setting, Purpose	Population Characteristics	Intervention and Comparator(s)	Relevant Clinical Outcomes, Length of Follow-Up
	in patients with impaired awareness of hypoglycemia and severe hypoglycemia events	• Weight ≤50 kg • Insulin requirement >1.0 units/kg/day or <15 units/day • HbA1c >10% • Measured GFR <80 mL/min/1.73m^2 • History of reactive anti-HLA antibodies by flow cytometry • Significant comorbid conditions **Median age:** 48 years **Median duration of diabetes:** 28.5 years **Median insulin requirement:** 32.6 units/day **Median serious hypoglycemic events in the past year:** 6.5 **Median HbA1c:** 7.2%		• hypoglycemic events • Proportion of participants with an HbA1c <7.0% • Median HbA1c • Proportion of participants experiencing at least one severe hypoglycemic event • Proportion of participants achieving insulin independence • Median insulin requirements **Follow-up:** 2 years
Lablanche, 2015[15] **France and Switzerland** **Funding:** The included studies received funding from ALFEDIAM, Association Française des Diabétigues, Aide aux Jeunes Diabétigues, Agir pour les Maladies chroniques, the PHRC from the French Ministry of Health and the Swiss National Foundation for Scientific Research	**Study design:** Before and after study using data from the GRAGIL-1c and GRAGIL-2 trials (N= 44) **Setting:** Multiple university hospitals within the GRAGIL network **Purpose:** To describe the 5-year outcome of islet transplantation in patients with type 1 diabetes from the GRAGIL-1c and GRAGIL-2 trials	The GRAGIL-1c trial included patients with type 1 diabetes with a functional kidney graft. **Inclusion criteria:** • Creatinine clearance >50 mL/min • Proteinuria <0.5 g/day • Daily insulin requirement <0.7 units/kg/day • BMI <26 kg/m^2 • Body weight <75 kg (male) or <70 kg (female) **Exclusion criteria:** • Liver and coagulation abnormalities • Unstable diabetic retinopathy • Poor cardiovascular prognosis The GRAGIL-2 trial included patients aged 18 to 65 years with type 1 diabetes for at least 5 years **Inclusion criteria:** • Negative C-peptide • Frequent episodes of severe hypoglycemia despite intensive insulin therapy **Exclusion criteria:**	**Intervention:** Islet cell transplantation consisting of up to three islet infusions **Comparator:** Baseline Pancreases were obtained from brain dead multiorgan donors. The mean total dose/kg was 9715.75 islet equivalents.	• Median HbA1c • Proportion of patients with an HbA1c ≤7% or experiencing a drop in HbA1c of ≥2% • Median fasting blood glucose • Mean number of severe hypoglycemic events/patient/year • Median insulin requirements • Proportion of patients attaining insulin independence **Follow-up:** 5 years

First Author, Publication Year, Country, Funding	Study Design, Setting, Purpose	Population Characteristics	Intervention and Comparator(s)	Relevant Clinical Outcomes, Length of Follow-Up
		• Kidney disease • Liver and coagulation abnormalities • Unstable ischemic diabetic retinopathy • Poor cardiovascular prognosis • BMI ≥26 kg/m^2 • Insulin requirement >0.7 units/kg/day **Median age:** 46 years **Median duration of diabetes:** 33 years **Median daily insulin requirements:** 0.5 units/kg **Median number of severe hypoglycemic events in the past year:** 5.5 **Median HbA1c:** 8.1%		

BMI = body mass index; CSII = continuous subcutaneous insulin infusion; GFR = glomerular filtration rate; HbA1c = glycated hemoglobin A1c; HIV = human immunodeficiency virus; MDI = multiple daily injections.

[a] = The modified β-score is based on the following variables: fasting glucose, fasting or stimulated C-peptide, HbA1c, and absence of insulin or oral hypoglycemic drug use. Up to two points are rewarded for each variable. As such, the score can range from 0 (no graft function) to 8 (optimal graft function). Contrary to the original β-score, the modified β-score does not assign an overall score of zero when stimulated C-peptide is negative.

[b] = The Clarke Score consists of questions on hypoglycemia awareness and the presence or absence on symptoms accompanying low blood glucose. The score can range from 0 to 8 where a score of 5 or higher indicates the presence of hypoglycemia unawareness.

[c] = The HYPOscore is a composite hypoglycemia score based on the frequency, severity and degree of unawareness of hypoglycemia. A HYPOscore of ≥1047 indicates serious problems with hypoglycemia.

Table 4: Characteristics of Included Economic Evaluation

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator	Clinical and Cost Data Used in Analysis	Main Assumptions
Wallner 2016[16] **Canada** **Funding:** Stem Cell Network grant and a Collaborative Research and	**Analysis:** Cost-utility analysis **Approach:** Model-based analysis (Markov Model)	To evaluate the cost-effectiveness of allogenic islet cell transplantation compared to	A hypothetical cohort of patients with unstable type 1 diabetes that met the transplantation inclusion criteria of the University of Alberta	**Intervention:** Islet cell transplantation **Comparator:** Intensive insulin therapy	**Clinical Inputs:** • Probability of patients experiencing initial complications • Probability of achieving insulin independence after the 1st, 2nd, 3rd, and 4th transplantation	• All patients without diabetes-related complications will have some graft survival in the cycle after transplantation

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator	Clinical and Cost Data Used in Analysis	Main Assumptions
Innovation Opportunities grant by Alberta Innovates Health Solutions	**Time Horizon:** Life-time horizon (62.5 years) **Cycle Length:** 1/16th of a year (~23 days) **Perspective:** Provincial health care payer (Alberta Health Services) **Discount Rate:** 5% per year **Cost Expression:** 2012 Canadian dollars **Analytic Approach:** Probabilistic analysis and structural sensitivity analysis	intensive insulin therapy.	Hospital (criteria not described). **Gender:** 55% female **Average age:** 47 years **Diabetes duration:** 29.4 years **Weight:** 71.1 kg **BMI:** 24.8 kg/m^2 **HbA1c:** 8.2% **Insulin requirements :** 0.6 units/kg/day		• Probabilities of patients getting diabetes-related complications with partial graft function and with full graft function • Probability of becoming partially insulin dependent with full graft function • Probability of graft failure after previous full graft function • Probability of graft failure within the first 6 months and after the first 6 for patients with partial graft function • Probability of major immunosuppressive related complications and the probability of ending immunosuppression because of the complications • Probability of additional diabetes related complications • Probability of background all-cause mortality • Probability of mortality due to hypoglycemia and mortality due to diabetes-related complications **Cost Inputs:** • Cost savings from reduced diabetes related complications • Costs savings from reduced insulin therapy • Short term increased cost from procedure itself including organ procurement, islet cell	• The proportion of patients with full graft function increased from the first to the third and fourth transplantation • Patients had a 55% risk of diabetes-related complications over the model horizon and these complications are reduced by 75% with full or partial graft function • Patients treated with intensive insulin therapy had a 12 years shorter life expectancy compared to the general, non-diabetic population • 65% of patients experienced minor and 1.5% of patients experienced major immunosuppressive complications • 10% of patients will stop immunosuppressive therapy because of complications • The price of generic

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator	Clinical and Cost Data Used in Analysis	Main Assumptions
					processing, transplantation procedure, follow-up visits, immunosuppression, and possible treatment of complications • Increased costs from resource use for graft survival including immunosuppression, clinical follow-up, insulin therapy and other medications **Utility Inputs:** • Full graft function with no complications • Partial graft function with no complications • Hypoglycemia unawareness • Diabetes-related complications (other than hypoglycemia unawareness)	immunosuppressant drugs was 1/3rd the cost of the brand name

BMI = body mass index; HbA1c = glycated hemoglobin A1c.

Table 5: Characteristics of Included Guideline

Intended Users, Target Population, Interventions	Relevant Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Diabetes Canada, 2018[3]					
Intended Users: Healthcare professionals involved in the management of patients with diabetes or prediabetes with a focus on primary care providers as well as Canadians living with diabetes **Target Population:** Canadians living with diabetes **Interventions:** Islet cell allotransplantation, islet cell autotransplantation after pancreatectomy, pancreas transplantation	Reduction or elimination of hypoglycemia, improvements in HbA1c, proportion of insulin independence	Systematic literature search by two health science librarians of relevant English-language, published, peer reviewed literature. Electronic databases were searched from September 2013 or later for previously included topics and since 1990 for new topics in the guideline and included searches of MEDLINE, EMBASE, CINAHL, the Cochrane Register of Trials and PsycINFO [where appropriate]. Screening was done in duplicate whereas full-text review was completed by a diabetes clinician and a methodologist.	**Level of Evidence:** • **1a:** SR or MA of high-quality RCTs • **1B:** Non-randomized clinical trial or cohort study with indisputable results • **2:** RCT or SR that does not meet Level 1 criteria • **3:** Non-randomized clinical trial or cohort study; SR or MA of Level 3 studies • **4:** Other **Grade of Recommendations:** • **A:** The best evidence was at Level 1 • **B:** The best evidence was at Level 2 • **C:** The best evidence was at Level 3 • **D:** The best evidence was at Level 4 or consensus	The relevant literature was evaluated by members of the Expert Committee who developed the guidelines and recommendations. If no new evidence was identified since the publication of the 2013 guidelines, recommendations from the 2013 document were not changed.	A draft document was externally peer reviewed by experts in relevant fields including specialists, community primary care providers, academic department of family medicine across Canada, and specialty and disease support organizations .

CINAHL = Cumulative Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica database; MA = meta-analysis; MEDLINE = Medical Literature Analysis and Retrieval System Online; PsycINFO = Psychological Information database; RCT = randomized controlled trial; SR = systematic review.

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of the Systematic Review using AMSTAR 2[6]

Strengths	Limitations
Health Quality Ontario, 2015[2]	
• The objective of the review was clearly stated • The eligible population, interventions and outcomes of the review were well defined • The inclusion and exclusion criteria were clearly described • Two databases (MEDLINE and EBM Reviews) were searched and reference lists from selected studies were also reviewed • Search strategies of the databases were provided and appropriate • A list of included studies was provided and the studies' characteristics were well described • The authors provided a GRADE quality score to each outcome of interest • Authors described heterogeneity across studies and the reason for not conducting a meta-analysis of the results • Authors disclosed that they had no conflicts of interest related to this review	• An *a priori* protocol was not reported for the review • The eligible comparators of the review were unclear • It was unclear if a search of the grey literature was performed • Study screening and selection were done by a single reviewer • It was unclear how data extraction was completed • Although reasons for the exclusion of studies were provided, a list of the excluded studies was not • Although the authors appraised the studies for quality, they did not consider the risk of bias for individual studies when interpreting and discussing results • Funding sources of included studies were not provided

EBM Reviews = Evidence-Based Medicine Reviews; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MEDLINE = Medical Literature Analysis and Retrieval System Online.

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[7]

Strengths	Limitations
Randomized Controlled Trial	
Lablanche, 2018[10]	
• The study addressed an appropriate and clearly focused research question • The inclusion and exclusion criteria were well defined and appropriate considering the study population and the research question • Patients recruited to the study appeared to be representative of the population of interest • The time period of patient recruitment was provided (June 2010 to July 2013) • The assignment of patients to the intervention and control arms was randomized (one to one ratio using a computer-generated randomization) • The intervention was well defined and included a description of the immunosuppression regimens • Estimates of random variability in the main outcomes were provided • The measured outcomes were clearly described • The statistical tests used to assess the main outcomes were described and appropriate	• The trial was open label for all participants, investigators and the statistician • Differences in baseline characteristics of the groups were present (i.e., fasting blood glucose, units of insulin administered per day) and no statistical testing or description of what would represent clinically meaningful differences was provided • The intervention of the insulin group was poorly described and may not have constituted intensive insulin therapy (i.e., the participants were asked to do at least four capillary glucose tests per day and to practice carbohydrate counting, insulin doses were adjusted every 3 months by the investigator) • Compliance with insulin regimens was not provided and the patients in the insulin group knew they would receive islet cell transplantations eventually, which may have influenced adherence • Although the trial was conducted in multiple hospitals, these French findings may not be generalizable to the Canadian setting

Strengths	Limitations
• A power calculation was included in which enrolling 32 participants yielded a 95% power to detect a difference between groups in the primary outcome (50 patients included in the trial) • Drop-out rates were low as only one participant in the intervention group and two in the control group did not receive their assigned interventions • Follow-up was well conducted as only one patient in the control group was lost to follow-up (died before receiving islet transplantation) • A list of adverse events was included • The trial had an *a priori* protocol and was registered (NCT01148680) • The funding source was declared (Programme Hospitalier de Recherche Clinique grant from the French Government), and they had no input in the design or conduct of the study • Authors declared conflicts of interest (none reported)	
Non-Randomized Studies	
Vantyghem et al., 2019[11]	
• The aim of the study was clearly described • The inclusion and exclusion criteria were well defined • Patient data were retrieved from 2 single-arm trials which were representative of the population of interest • The time period of patient recruitment was provided (March 2003 to December 2012) • The intervention was well defined and included a description of the immunosuppression regimens • Estimates of random variability in the main outcomes were provided • The measured outcomes were clearly described • The statistical tests used to assess the main outcomes were described and appropriate • The authors used an intention-to-treat analysis to report results • Characteristics of patients lost to follow-up were provided • A list of adverse events was included • Authors conflicts of interest were provided (none reported) • Funding sources were provided	• It was unclear how the included trials calculated the sample sizes which were small (N=14 each) • Although baseline characteristics were provided, including exogenous insulin requirements, it was unclear what types of insulins, insulin regimens, or regimens of blood glucose level monitoring were used and how patients calculated insulin requirements (therefore the “insulin therapy” comparison was unclear) • As patients were first recruited in 2003, it was unclear if newer technologies (e.g., hybrid closed loop insulin delivery systems) would have provided the patients better glycemic control • At 10 years, 8 patients (29%) were not followed-up • The studies were conducted at a single center in France and may not be generalizable to the Canadian context
Foster et al., 2018[12]	
• The aim of the study was clearly described • Estimates of random variability in the main outcomes were provided • The measured outcomes were clearly described • The statistical tests used to assess the main outcomes were described and appropriate • P-values were adjusted for multiple comparisons using the false discovery rate approach • Authors conflicts of interest were provided • Funding sources were provided	• Although four unique questionnaires were utilized, certain issues that can affect patients’ quality of life (e.g., the need for lifelong immunosuppression) may not have been properly captured • Although baseline characteristics were provided, including exogenous insulin requirements, it was unclear what types of insulins, insulin regimens, or regimens of blood glucose level monitoring were used and how patients calculated insulin requirements (therefore the “insulin therapy” comparison was unclear)

Strengths	Limitations
Note: This study utilized the data from Hering et al., 2016[14] and referenced it for key information. For additional strengths and limitations (i.e., pertaining to population inclusion and exclusion criteria, population baseline characteristics, time period of patient recruitment, details of the intervention, sample size calculation) see Hering et al., 2016[14]	• As patients were first recruited in 2008, it was unclear if newer technologies (e.g., hybrid closed loop insulin delivery systems) would have provided the patients better glycemic control • At 2 years, up to 15 patients (34%) were lost to follow-up in some outcomes • Characteristics of patients lost to follow-up were not provided • The study was conducted at multiple centers in the United States and may not be generalizable to the Canadian context
Holmes-Walker et al., 2017[13]	
• The aim of the study was clearly described • Patient data were retrieved from 2 single-arm trials which appear to be representative of the population of interest • The time period of patient recruitment was provided (January 2006 to December 2010) • The intervention and immunosuppression regimens were not specifically detailed, but were reported in the referenced studies • Although only briefly described, there was an attempt to optimize insulin therapy and provide dietician and regular endocrinologist review prior to transplantation • Estimates of random variability in the main outcomes were provided • The measured outcomes were clearly described • The statistical tests used to assess the main outcomes were described and appropriate • A list of adverse events was included • Authors conflicts of interest were provided (none reported) • Funding sources were provided	• Although the study referenced the two studies from which participants' data was pulled, the inclusion and exclusion criteria were not specifically clear: the study included 10 participants whereas the two referenced studies had N=23 • Although baseline characteristics were provided, including exogenous insulin requirements, it was unclear what types of insulins, insulin regimens, or regimens of blood glucose level monitoring were used and how patients calculated insulin requirements (therefore the "insulin therapy" comparison was unclear) • As patients were first recruited in 2006, it was unclear if newer technologies (e.g., hybrid closed loop insulin delivery systems) would have provided the patients better glycemic control • The studies were conducted at two centers in Australia and may not be generalizable to the Canadian context
Hering et al., 2016[14]	
• The aim of the study was clearly described • The inclusion and exclusion criteria were well defined • Patients recruited to the study appeared to be representative of the population of interest • The time period of patient recruitment was provided (the first patient consented in October 2008) • The intervention was well defined and included a description of the immunosuppression regimens • Estimates of random variability in the main outcomes were provided • The measured outcomes were clearly described • The statistical tests used to assess the main outcomes were described and appropriate • A sample size calculation was provided (assuming a true rate of success for the primary endpoint of at least 70%, 48 participants allow for an at least 84% power to declare islet transplantation effective) • P-values were adjusted for multiple comparisons using the Bonferroni method	• Although baseline characteristics were provided, including exogenous insulin requirements, it was unclear what types of insulins, insulin regimens, or regimens of blood glucose level monitoring were used and how patients calculated insulin requirements (therefore the "insulin therapy" comparison was unclear) • As patients were first recruited in 2008, it was unclear if newer technologies (e.g., hybrid closed loop insulin delivery systems) would have provided the patients better glycemic control • At 2 years, 8 patients (17%) were lost to follow-up • The study was conducted at multiple centers in the United States and may not be generalizable to the Canadian context

Strengths	Limitations
• The authors used an intention-to-treat analysis to report results • Characteristics of patients lost to follow-up were provided • A list of adverse events was included • The trial had an *a priori* protocol and was registered (NCT00434811) • Authors conflicts of interest were provided • Funding sources were provided	
Lablanche et al., 2015[15]	
• The aim of the study was clearly described • The inclusion and exclusion criteria were well defined • Patient data were retrieved from 2 single-arm trials which appear to be representative of the population of interest • The time period of patient recruitment was provided (September 2003 to April 2010) • The intervention was well defined and included a description of the immunosuppression regimens • Estimates of random variability in the main outcomes were provided • The measured outcomes were clearly described • A list of adverse events was included • Authors conflicts of interest were provided (none reported) • Funding sources were provided	• The statistical tests used to assess the main outcomes were not described • P-values were provided; however, it was unclear which data they were attributed with as a single p-value was provided after sets of multiple outcome measurements • Although baseline characteristics were provided including exogenous insulin requirements, it was unclear what types of insulins, insulin regimens, or regimens of blood glucose level monitoring were used and how patients calculated insulin requirements (therefore the "insulin therapy" comparison was unclear) • As patients were first recruited in 2003, it was unclear if newer technologies (e.g., hybrid closed loop insulin delivery systems) would have provided the patients better glycemic control • The studies were conducted at multiple centers in France and Switzerland. They may not be generalizable to the Canadian context

Table 8: Strengths and Limitations of Economic Studies using the Drummond Checklist[8]

Strengths	Limitations
Wallner et al., 2016[16]	
• The research question was clearly stated • The economic importance of the research question was stated • The perspective of the analysis was clearly stated and justified • The treatment alternatives being compared were clearly described • The form of economic evaluation used was stated • The sources of effectiveness estimates used were stated • The primary outcome measures for the economic evaluation were clearly stated • Currency and price data were recorded • Details of the model used were provided and the choice of model used and the key parameters on which it was based were justified • The time horizon of costs and benefits was stated	• The choice of form of economic evaluation was not justified in relation to the question addressed • Details of the design and results of effectiveness studies were not provided • Quantities of resource use were not reported separately from their unit costs • Methods for the estimation of quantities and unit costs were not described • Details of currency of price adjustments for inflation were not provided

Strengths	Limitations
• The discount rate was stated and the choice of discount rate was justified • The approach to the sensitivity analysis was provided • The choice of variables for the sensitivity analysis was justified • Major outcomes were presented in a disaggregated as well as an aggregated form • The answer to the study question was provided • Conclusions followed from the data reported and conclusions were accompanied by appropriate caveats • Funding sources of the evaluation were provided and conflicts of interest declared (none)	

Table 9: Strengths and Limitations of Guidelines using AGREE II[9]

Item	Guideline
	Diabetes Canada, 2018[3]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	No - but the intent was easily perceived
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes
14. A procedure for updating the guideline is provided.	Yes
Domain 4: Clarity of Presentation	

Item	Guideline
	Diabetes Canada, 2018[3]
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	No
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 10: Summary of Findings Included Systematic Review

Main Study Findings	Authors' Conclusion
Health Quality Ontario, 2015[2]	
Note: The SR summarized the body of evidence for each outcome, and assigned quality scores according to the GRADE Working Group criteria as High, Moderate, Low or Very Low[a]. Findings from case series and observational comparative studies were pooled for each outcome. **Non-Uremic Patients** <u>Islet transplantation alone compared to baseline prior to transplantation in case series or intensive insulin therapy in observational comparative studies:</u> Improved glycemic control (GRADE: Low to High) • Improved graft loss/insulin independence (15 studies; GRADE: High) • Improved HbA1c (15 studies; GRADE: Low) • Reduction in insulin requirements (11 studies; GRADE: Low) • Improved hypoglycemia events/unawareness (9 studies; GRADE: Low) Improved secondary complications of diabetes (GRADE: Very Low to Low) • Improved cardiovascular disease (4 studies; GRADE: Very Low) • Improved retinopathy (5 studies; GRADE: Low) • Improved nephropathy (6 studies; GRADE: Very Low) • Improved neuropathy (5 studies; GRADE: Very Low) Increased procedure-related and immunosuppression-related adverse events (21 studies; GRADE: Low) Improved health-related quality of life (12 studies; GRADE: Very Low) **Uremic Patients** <u>Islet after kidney transplantation and simultaneous islet-kidney transplantation compared to baseline prior to transplantation in case series or intensive insulin therapy in observational comparative studies:</u> Improved glycemic control (GRADE: Low to High) • Improved graft loss/insulin independence (7 studies; GRADE: High) • Improved HbA1c (8 studies; GRADE: Very Low) • Reduction in insulin requirements (8 studies; GRADE: Low) • Improved hypoglycemia events/unawareness (2 studies; GRADE: Low) Improved secondary complications of diabetes (GRADE: Low)	*"Islet transplantation offers an alternative for patients with type 1 diabetes who have brittle diabetes with difficult-to-control blood glucose levels or hypoglycemic unawareness despite optimal insulin therapy."* (p. 67)

Main Study Findings	Authors' Conclusion
• Improved cardiovascular risk factors (6 studies; GRADE: Low) • Improved nephropathy (6 studies; GRADE: Low) Increased procedure-related and immunosuppression-related adverse events (5 studies; GRADE: Low) Improved health-related quality of life (2 studies; GRADE: Very Low)	

HbA1c = glycated hemoglobin A1c; GRADE = Grading of Recommendations Assessment, Development and Evaluation; SR = systematic review.

[a] = High: the true effect lies close to the estimate of the effect; Moderate: the true effect is most likely close, but may also be substantially different than the estimate of the effect; Low: the true effect may be substantially different than the estimate of the effect; Very Low: the true effect is likely to be substantially different than the estimate of the effect.

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trial	
Lablanche, 2018[10]	
Primary outcome: Proportion of participants with a modified β-score[a] of 6 or higher (islet transplantation group vs. insulin therapy group): 64% (95% CI, 43 to 82) vs. 0% (95% CI, 0 to 15), P < 0.0001 **Secondary outcomes:** Median HbA1c (islet transplantation group vs. insulin therapy group): 5.6% vs. 8.2%, P < 0.0001 (IQRs not provided) Median fasting blood glucose level (islet transplantation group vs. insulin therapy group): 5.9 mmol/L (IQR, 5.2 to 6.7) vs. 5.7 mmol/L (IQR, 4.9 to 10.9), P = 0.92 Proportion of participants with an HbA1c <7% without severe hypoglycemia (islet transplantation group vs. insulin therapy group): 84% (95% CI, 64 to 96) vs. 0% (95% CI, 0 to 15), P < 0.0001 Median number of severe hypoglycemia events per year (islet transplantation group vs. insulin therapy group): 0 (IQR, 0 to 0) vs. 2 (IQR, 0 to 4), P < 0.0001 Proportion of participants free from severe hypoglycemia (islet transplantation group vs. insulin therapy group): 92% (95% CI, 74 to 99) vs. 36% (95% CI, 17 to 59), P < 0.0001 Median number of non-severe hypoglycemia events per year (islet transplantation group vs. insulin therapy group): 0 (IQR, 0 to 0) vs. 5 (IQR, 0 to 17), P < 0.0003 Median insulin requirements (numerical data not provided): Statistically significant improvement with immediate islet transplantation compared to insulin group, P < 0.0001	*"Although studies with longer-term follow-up are needed, our findings suggest that islet transplantation is a valid option for patients with severe, unstable type 1 diabetes who are not responding to intensive medical treatments."* (p. 535) *"In conclusion, the results of the TRIMECO trial suggest that, compared with insulin therapy, islet transplantation is an effective intervention in patients with severe forms of type 1 diabetes. We suggest that islet transplantation should be integrated into the stepped-care approach for the treatment of such patients."* (p. 536)

Main Study Findings	Authors' Conclusion
Median gain in quality of life dimensions assessed with the Diabetes Quality of Life questionnaire (numerical data not provided): Statistically significant improvement with immediate islet transplantation compared to insulin group in Satisfaction (P < 0.0001), Impact of Diabetes (P < 0.0001), Diabetes-Related Worry (P = 0.005) and Global Score (P < 0.0001) No statistically significant difference with immediate islet transplantation compared to insulin group in Wellbeing (P = 0.21) No statistical analysis conducted in Social Worry category because of the low number of respondents for this item Median gain in quality of life dimensions assessed with the Short Form 36 Health Survey (numerical data not provided): Statistically significant improvement with immediate islet transplantation compared to insulin group in General Health (P = 0.008) and Health Transition (P = 0.0006) No statistically significant difference with immediate islet transplantation compared to insulin group in Physical Functioning (P = 0.20), Physical Role Limitations (P = 0.91), Bodily Pain (P = 0.82), Vitality (P = 0.08), Social Functioning (P = 0.58), Emotional Role Limitations (P = 0.70), Mental Health (P = 0.14), Physical Component Score (P = 0.08), Mental Component Score (P = 0.67) **Outcomes assessed at 12 months after the first infusion in the full cohort (islet transplantation group compared to baseline):** Modified β-score[a] of 6 or higher: 63% (95% CI, 48 to 77) vs. 0%, P < 0.0001 Median HbA1c: 5.8% (IQR, 5.5 to 6.7) vs. 8.1% (IQR, 7.4 to 8.9), P < 0.0001 Median fasting blood glucose level: 5.7 mmol/L (IQR, 5.2 to 7.3) vs. 9.1 mmol/L (IQR, 5.9 to 13.0), P = 0.0002 Proportion of participants with an HbA1c <7% without severe hypoglycemia: 70% (95% CI, 54 to 82) vs. 2% (95% CI, 0 to 11), P < 0.0001 Median number of severe hypoglycemia events per year: 0 (IQR, 0 to 0) vs. 2 (IQR, 0 to 4), P < 0.0001 Proportion of participants free from severe hypoglycemia: 85% (95% CI, 71 to 94) vs. 34% (95% CI, 21 to 49), P < 0.0001 Median number of non-severe hypoglycemia events per patient year: 0 (IQR, 0 to 0) vs. 10 (IQR, 4 to 17), P < 0.0001 Median Clarke Score[b]: 0 (IQR, 0 to 2) vs. 5 (IQR, 3 to 6), P < 0.0001 Proportion of participants achieving insulin independence: 59% (95% CI, 43 to 73, P < 0.0001 vs. baseline) Median insulin requirements (numerical data not provided): Statistically significant improvement with islet cell transplantation compared to baseline, P < 0.0001	

Main Study Findings	Authors' Conclusion
Adverse events: Infections and infestations (43%), gastrointestinal disorders (39%), blood and lymphatic system disorders (35%), procedural complications (20%), nervous system disorders (17%), renal and urinary disorders (13%), cardiac disorders (11%), metabolism and nutrition disorders (13%)	
Non-Randomized Studies	
Vantyghem, 2019[11]	
Primary Outcome Proportion of patients achieving insulin independence following islet transplantation: 5 years: 39% (95% CI, 22 to 57) 10 years: 28% (95% CI, 13 to 45) **Secondary Outcomes** Median number of severe hypoglycemia events in previous year (following islet transplantation vs. baseline): 1 year: 0 (IQR, 0 to 0) vs. 2 (IQR, 1 to 5), P < 0.0001 5 years: 0 (IQR, 0 to 0) vs. 2 (IQR, 1 to 5), P < 0.0001 10 years: 0 (IQR, 0 to 0) vs. 2 (IQR, 1 to 5), P < 0.0001 Median HbA1c (following islet transplantation vs. baseline): 1 year: 5.9% (IQR, 5.5 to 6.7) vs. 8.15% (IQR, 7.3 to 8.95), P < 0.0001 5 years: 6.9% (IQR, 6.1 to 7.5) vs. 8.15% (IQR, 7.3 to 8.95), P < 0.0001 10 years: 6.7% (IQR, 6.1 to 8.0) vs. 8.15% (IQR, 7.3 to 8.95), P = 0.0009 Median exogenous insulin requirements (following islet transplantation vs. baseline): 1 year: 0 units/kg/day (IQR, 0 to 0.04) vs. 0.57 units/kg/day (IQR, 0.41 to 0.74), P < 0.0001 5 years: 0 units/kg/day (IQR, 0 to 0.36) vs. 0.57 units/kg/day (IQR, 0.41 to 0.74), P < 0.0001 10 years: 0.28 units/kg/day (IQR, 0 to 0.43) vs. 0.57 units/kg/day (IQR, 0.41 to 0.74), P < 0.0001 Median mean glucose via continuous glucose monitoring (following islet transplantation vs. baseline): 1 year: 112 mg/dL (IQR, 102 to 133) vs. 146 mg/dL (IQR, 131 to 208), P < 0.0001 5 years: 126 mg/dL (IQR, 110 to 144) vs. 146 mg/dL (IQR, 131 to 208), P < 0.0001 10 years: 118 mg/dL (IQR, 113 to 154) vs. 146 mg/dL (IQR, 131 to 208), P = 0.0007 Median standard deviation of mean glucose via continuous glucose monitoring (following islet transplantation vs. baseline): 1 year: 22 mg/dL (IQR, 15 to 41) vs. 63 mg/dL (IQR, 45 to 77), P < 0.0001 5 years: 29 mg/dL (IQR, 17 to 52) vs. 63 mg/dL (IQR, 45 to 77), P < 0.0001 10 years: 40 mg/dL (IQR, 18 to 54) vs. 63 mg/dL (IQR, 45 to 77), P < 0.0001 Median percentage of time spent below range (<70 mg/dL) (following islet transplantation vs. baseline): 1 year: 0% (IQR, 0 to 5) vs. 9% (IQR, 3 to 16), P < 0.0001 5 years: 1% (IQR, 0 to 3) vs. 9% (IQR, 3 to 16), P < 0.0001 10 years: 3% (IQR, 0 to 9) vs. 9% (IQR, 3 to 16), P = 0.0012 Adverse events: During the first year post-transplantation: 11 adverse events related to the infusion procedure, 5 adverse events related to immunosuppression (hematological disorders, infections, diarrhea) From 1 year to 10 years post-transplantation: 8 adverse events related to immunosuppression (infections, skin carcinomas)	*"To conclude, the current study provides direct evidence that islet transplantation performed alone or after a kidney graft in patients with type 1 diabetes can markedly improve metabolic control and suppress SHEs during 10 years."* (p. 2048)

Main Study Findings	Authors' Conclusion
Foster, 2018[12]	
Note: The effect size was calculated as the mean change from baseline divided by the baseline standard deviation. **Condition Specific Health Related Quality of Life: Diabetes Distress Scale** Total score: Baseline (Mean, Standard deviation): 2.62, 0.98 Day 75 (Mean, Effect size, P-value): 1.83, -0.80, < 0.0001 Day 365 (Mean, Effect size, P-value): 1.50, -1.22, < 0.0001 Day 730 (Mean, Effect size, P-value): 1.32, -1.33, < 0.0001 Emotional Burden: Baseline (Mean, Standard deviation): 3.75, 1.31 Day 75 (Mean, Effect size, P-value): 2.59, -0.83, < 0.0001 Day 365 (Mean, Effect size, P-value): 1.85, -1.48, < 0.0001 Day 730 (Mean, Effect size, P-value): 1.43, -1.79, < 0.0001 Physician-Related Distress: Baseline (Mean, Standard deviation): 1.67, 1.02 Day 75 (Mean, Effect size, P-value): 1.19, -0.47, < 0.0001 Day 365 (Mean, Effect size, P-value): 1.06, -0.58, < 0.0001 Day 730 (Mean, Effect size, P-value): 1.10, -0.51, = 0.0013 Regimen-Related Distress: Baseline (Mean, Standard deviation): 2.66, 1.20 Day 75 (Mean, Effect size, P-value): 1.77, -0.78, < 0.0001 Day 365 (Mean, Effect size, P-value): 1.61, -0.94, < 0.0001 Day 730 (Mean, Effect size, P-value): 1.42, -1.05, < 0.0001 Interpersonal Distress: Baseline (Mean, Standard deviation): 2.19, 1.38 Day 75 (Mean, Effect size, P-value): 1.59, -0.42, = 0.0002 Day 365 (Mean, Effect size, P-value): 1.47, -0.55, < 0.0001 Day 730 (Mean, Effect size, P-value): 1.35, -0.70, < 0.0001 **Hypoglycemic Fear Survey** Total score: Baseline (Mean, Standard deviation): 2.36, 0.66 Day 75 (Mean, Effect size, P-value): 1.33, -1.51, < 0.0001 Day 365 (Mean, Effect size, P-value): 0.54, -2.59, < 0.0001 Day 730 (Mean, Effect size, P-value): 0.41, -2.85, < 0.0001 Hypoglycemic Avoidance Behavior: Baseline (Mean, Standard deviation): 2.52, 0.54 Day 75 (Mean, Effect size, P-value): 1.47, -1.86, < 0.0001 Day 365 (Mean, Effect size, P-value): 0.64, -3.34, < 0.0001 Day 730 (Mean, Effect size, P-value): 0.67, -3.31, < 0.0001 Worry About Hypoglycemia: Baseline (Mean, Standard deviation): 2.20, 0.90 Day 75 (Mean, Effect size, P-value): 1.27, -1.13, < 0.0001 Day 365 (Mean, Effect size, P-value): 0.53, -1.79, < 0.0001 Day 730 (Mean, Effect size, P-value): 0.47, -1.88, < 0.0001	*"These patient-reported outcomes corroborate the clinical importance of the objective benefits of islet transplantation already documented in the CIT-07."* (p. 1007)

Main Study Findings	Authors' Conclusion
Functional Health Status and Health Utility: **Short Form 36 Health Survey** Physical Component Summary: Baseline (Mean, Standard deviation): 47.52, 8.77 Day 75 (Mean, Effect size, P-value): 49.97, 0.31, NS Day 365 (Mean, Effect size, P-value): 52.52, 0.54, < 0.0001 Day 730 (Mean, Effect size, P-value): 52.44, 0.39, = 0.0004 Mental Component Summary: Baseline (Mean, Standard deviation): 49.23, 10.48 Day 75 (Mean, Effect size, P-value): 53.03, 0.28, = 0.0081 Day 365 (Mean, Effect size, P-value): 51.86, 0.28, NS Day 730 (Mean, Effect size, P-value): 54.40, 0.30, NS Physical Functioning Scale: Baseline (Mean, Standard deviation): 50.62, 8.04 Day 75 (Mean, Effect size, P-value): 53.30, 0.29, = 0.0034 Day 365 (Mean, Effect size, P-value): 53.67, 0.35, = 0.0005 Day 730 (Mean, Effect size, P-value): 52.29, 0.19, NS Role Physical Scale: Baseline (Mean, Standard deviation): 45.69, 10.57 Day 75 (Mean, Effect size, P-value): 49.17, 0.31, = 0.0008 Day 365 (Mean, Effect size, P-value): 51.70, 0.57, < 0.0001 Day 730 (Mean, Effect size, P-value): 52.67, 0.48, < 0.0001 Bodily Pain Scale: Baseline (Mean, Standard deviation): 50.52, 10.04 Day 75 (Mean, Effect size, P-value): 49.96, -0.05, NS Day 365 (Mean, Effect size, P-value): 52.72, 0.22, NS Day 730 (Mean, Effect size, P-value): 53.22, 0.08, NS General Health Scale: Baseline (Mean, Standard deviation): 44.31, 12.42 Day 75 (Mean, Effect size, P-value): 50.19, 0.49, < 0.0001 Day 365 (Mean, Effect size, P-value): 51.57, 0.57, < 0.0001 Day 730 (Mean, Effect size, P-value): 51.60, 0.39, = 0.0064 Vitality Scale: Baseline (Mean, Standard deviation): 48.81, 10.94 Day 75 (Mean, Effect size, P-value): 54.67, 0.51, = 0.0001 Day 365 (Mean, Effect size, P-value): 53.38, 0.40, = 0.0029 Day 730 (Mean, Effect size, P-value): 55.38, 0.44, = 0.0015 Social Functioning Scale: Baseline (Mean, Standard deviation): 46.99, 10.78 Day 75 (Mean, Effect size, P-value): 49.38, 0.19, NS Day 365 (Mean, Effect size, P-value): 50.98, 0.30, NS Day 730 (Mean, Effect size, P-value): 51.70, 0.28, NS Role Emotional Scale: Baseline (Mean, Standard deviation): 48.02, 10.25 Day 75 (Mean, Effect size, P-value): 51.58, 0.20, NS Day 365 (Mean, Effect size, P-value): 50.82, 0.31, = 0.0090 Day 730 (Mean, Effect size, P-value): 52.11, 0.25, NS	

Main Study Findings	Authors' Conclusion
Mental Health Scale: Baseline (Mean, Standard deviation): 53.48, 15.70 Day 75 (Mean, Effect size, P-value): 56.10, 0.21, NS Day 365 (Mean, Effect size, P-value): 55.12, 0.28, NS Day 730 (Mean, Effect size, P-value): 57.41, 0.22, NS **EuroQoL 5 Dimensions** Visual Analogue Scale: Baseline (Mean, Standard deviation): 74.13, 14.66 Day 75 (Mean, Effect size, P-value): 79.06, 0.29, NS Day 365 (Mean, Effect size, P-value): 82.86, 0.71, < 0.0001 Day 730 (Mean, Effect size, P-value): 85.74, 0.73, < 0.0001 Health Preference Weight: Baseline (Mean, Standard deviation): 0.87, 0.12 Day 75 (Mean, Effect size, P-value): 0.86, -0.06, NS Day 365 (Mean, Effect size, P-value): 0.86, -0.04, NS Day 730 (Mean, Effect size, P-value): 0.88, 0.009, NS Usual Activities: Baseline (Percent "No Problems" responses): 68.09% Day 75 (Percent "No Problems" responses, P-value): 74.47%, NS Day 365 (Percent "No Problems" responses, P-value): 78.57%, NS Day 730 (Percent "No Problems" responses, P-value): 84.38%, NS Anxiety/Depression: Baseline (Percent "No Problems" responses): 68.09% Day 75 (Percent "No Problems" responses, P-value): 72.34%, NS Day 365 (Percent "No Problems" responses, P-value): 69.05%, NS Day 730 (Percent "No Problems" responses, P-value): 71.88%, NS Mobility: Baseline (Percent "No Problems" responses): 80.85% Day 75 (Percent "No Problems" responses, P-value): 85.11%, NS Day 365 (Percent "No Problems" responses, P-value): 82.93%, NS Day 730 (Percent "No Problems" responses, P-value): 81.25%, NS Pain/Discomfort: Baseline (Percent "No Problems" responses): 53.19% Day 75 (Percent "No Problems" responses, P-value): 57.45%, NS Day 365 (Percent "No Problems" responses, P-value): 57.14%, NS Day 730 (Percent "No Problems" responses, P-value): 68.75%, NS Self-Care: Baseline (Percent "No Problems" responses): 95.74% Day 75 (Percent "No Problems" responses, P-value): 97.87%, NS Day 365 (Percent "No Problems" responses, P-value): 92.86%, NS Day 730 (Percent "No Problems" responses, P-value): 90.63%, NS	
Holmes-Walker, 2017[13]	
Average insulin requirements (12-months post-islet transplantation vs. CSII) (no statistical comparison provided): 0.2 ±0.2 IU/kg vs. 0.4 ±0.2 IU/kg	*"In our study, islet transplantation was the only treatment which reduced severe hypoglycemia to near-*

Main Study Findings	Authors' Conclusion
Average HbA1c (12-months post-islet transplantation vs. CSII): 6.4 ±1.3% vs. 8.2 ±1.8%, P = 0.01 Median HYPOscore[c] (12-months post-islet transplantation vs. CSII): 0 (IQR, 0 to 1) vs. 1085 (IQR, 622 to 1400), P < 0.01 Median hypoglycemic events per person year (12-months post-islet transplantation vs. CSII): 0 (IQR, 0 to 1) vs. 8 (IQR, 0 to 18), P < 0.05 Median percentage of time with glucose less than 4 mmol/L (12-months post-islet transplantation vs. CSII): 0% (IQR, 0 to 1) vs. 1% (IQR, 1 to 8) (no P-value provided, but authors stated no statistically significant difference) Median percentage of time with glucose between 4 to 8 mmol/L (12-months post-islet transplantation vs. CSII): 81% (IQR, 71 to 95) vs. 48.5% (IQR, 44 to 66), P < 0.01 Average blood glucose level via continuous glucose monitoring (12-months post-islet transplantation vs. CSII): 7.1 ±1.9 mmol/L vs. 8.8 ±1.9 mmol/L (no P-value provided, but authors stated no statistically significant difference) Average standard deviation of blood glucose level (12-months post-islet transplantation vs. CSII): 1.7 ±0.8 mmol/L vs. 3.2 ±1.1 mmol/L, P = 0.01 Continuous overlapping net glycemic action 4-hour interval (no numerical data provided): Significantly reduced in 12 months post-islet transplantation vs CSII, P = 0.04 Adverse events: Transient lymphopenia in 4 patients, >20% reduction in glomerular filtration rate in 2 patients	*normal and improved HbA1c. The present study is further evidence that in appropriately selected patients with severe hypoglycemia with large glycemic variability, islet transplantation provides superior control and reduction in hypoglycemia over and above that achieved with CSII and therefore has the potential to have a greater impact on survival and long-term complications."* (p. 1273-1274)
Hering, 2016[14]	
Primary outcome Proportion of participants with an HbA1c <7.0% with eradication of severe hypoglycemic events following islet transplant: Day 365: 87.5%, lower boundary of CI 76.8%, P < 0.001 Day 730: 71%, P< 0.01 (confidence interval not provided) Note: For the primary endpoint, a one-sided 95% lower confidence bound was calculated and the prespecified criterion for efficacy was that the lower bound be >50%. **Secondary outcomes** Proportion of participants with an HbA1c <6.5% with eradication of severe hypoglycemic events following islet transplant: Day 365: 79.1%, P < 0.001 (confidence interval not provided) Day 730: 68.8%, P = 0.02 (confidence interval not provided) Proportion of participants with an HbA1c <7.0% (islet cell transplantation vs. baseline): Day 75: 87.5% vs. 40%, P < 0.0003 Day 365: 87.5% vs. 40%, P < 0.0003 Median HbA1c (islet cell transplantation vs. baseline): Day 75: 5.9% vs. 7.2%, P < 0.0003	*"In conclusion, this trial demonstrates that transplantation of human islets is an effective treatment for T1D complicated by IAH and SHEs, resulting in the restoration of hypoglycemia awareness, elimination of SHEs, and normal or near-normal glycemic control in 87.5% of participants. Islet transplantation should be considered for patients with T1D and IAH in whom a stepped-care approach, including current educational, pharmacological, and technological interventions, has failed to prevent life-threatening SHEs."* (p. 1238)

Main Study Findings	Authors' Conclusion
Day 365: 5.2% vs. 7.2%, P < 0.0003 Proportion of participants experiencing at least one severe hypoglycemic event: 2 of 45 in post islet transplantation vs 48 of 48 baseline, P < 0.0003 Proportion of participants achieving insulin Independence following islet transplant: Day 75: 23% Day 365: 52.1% Day 730: 42% Median insulin requirements (islet cell transplantation vs. baseline): Day 75: 0.13 units/kg vs. 0.49 units/kg, P < 0.0003 Day 365: 0.00 units/kg vs. 0.49 units/kg, P < 0.0003 **Other outcomes** Measures of hypoglycemia awareness, hypoglycemic events and glycemic lability/variability using the Clarke score[b], HYPOscore[c] and mean amplitude of glycemic excursions: All improved significantly compared to baseline, P < 0.0002 (numerical data not provided) Adverse events: 30 serious adverse events occurred in year 1, 22 of which were procedure related bleeding events or immunosuppression related events including cytopenia, abdominal pain, toxic drug levels, infections and renal dysfunction 8 serious adverse events occurred in year 2, 2 of which were immunosuppression related events (infections)	
Lablanche, 2015[15]	
Median HbA1c: 6.20% (IQR, 4.60 to 9.60), 6.60% (IQR, 5.50 to 9.40), and 6.70% (IQR, 5.40 to 9.60) at 12, 48, and 60 months respectively post islet transplantation vs. 8.1% (IQR, 7.60 to 9.00) at baseline, P < 0.05 Proportion of patients with an HbA1c ≤7% or experiencing a drop in HbA1c of ≥2%: 84%, 70%, and 59% at 12, 48 and 60 months respectively post islet transplantation vs. 9% before islet infusion, P < 0.005 Median fasting blood glucose: 6.44 mmol/L (IQR, 4.11 to 11.3), 6.57 mmol/L (IQR, 3.4 to 11.8), and 7.28 mmol/l (IQR, 4.1 to 15.1) at 12, 48, and 60 months respectively post islet transplantation vs. 8.19 mmol/L (IQR, 1.56 to 22.4) at baseline, P < 0.05 Mean number of severe hypoglycemia (throughout 5-year follow up): 0 events/patient/year in the islet transplantation alone recipients and 0.01 events/patient/year in the islet after kidney transplant recipients, P < 0.005 (vs. baseline [not reported]) Median insulin requirements: 0.15 units/kg/day (IQR, 0 to 0.47), 0.17 units/kg/day (IQR, 0 to 0.7) and 0.18 units/kg/day (IQR, 0 to 0.57) at 12, 48, and 60 months respectively post islet transplantation vs. 0.50 units/kg/day (IQR, 0.42 to 0.58) at baseline, P < 0.05 Proportion of patients attaining insulin independence: 45%, 40%, 40%, 35%, and 31.5% at 12, 24, 36, 48, and 60 months in islet after kidney transplant recipients	*"In conclusion, islet transplantation within the multicenter GRAGIL Network provided important and lasting clinical benefits to patients with type 1 diabetes, permitting improvement of glucose variability and preventing the occurrence of severe hypoglycemia."* (p. 1721)

Main Study Findings	Authors' Conclusion
37.5%, 45.8%, 37.5%, 25%, and 14% at 12, 24, 36, 48, and 60 months respectively in islet transplantation alone recipients Adverse events: Related to the infusion procedure (1 cytolysis, 1 abdominal pain, 1 segmental portal vein thrombosis, 7 hemorrhages) or to immunosuppression (18 adverse events)	

CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA1c = glycated hemoglobin A1c; IAH = impaired awareness hypoglycemia; IQR = interquartile range; NS = not statistically significant; SHEs = severe hypoglycemia events; T1D = type 1 diabetes.

[a] = The modified β-score is based on the following variables: fasting glucose, fasting or stimulated C-peptide, HbA1c, and absence of insulin or oral hypoglycemic drug use. Up to two points are rewarded for each variable. As such, the score can range from 0 (no graft function) to 8 (optimal graft function). Contrary to the original β-score, the modified β-score does not assign an overall score of zero when stimulated C-peptide is negative.

[b] = The Clarke Score consists of questions on hypoglycemia awareness and the presence or absence on symptoms accompanying low blood glucose. The score can range from 0 to 8 where a score of 5 or higher indicates the presence of hypoglycemia unawareness.

[c] = The HYPOscore is a composite hypoglycemia score based on the frequency, severity and degree of unawareness of hypoglycemia. A HYPOscore of ≥1047 indicates serious problems with hypoglycemia.

Table 12: Summary of Findings of Included Economic Evaluation

Main Study Findings	Authors' Conclusion
Wallner et al., 2016[16]	
Base-case probabilistic analysis (assuming a 12 year difference in life expectancy caused by hypoglycemia): Costs: Standard care: $56,560 Islet cell transplantation: $347,377 Cost difference: $290,816 QALYs: Standard care: 9.59 Islet cell transplantation: 11.52 Benefit difference: 1.94 ICER: $150,006 per QALY gained Analysis: 95% probability of being cost-effective at a willingness-to-pay threshold of $196,000 13% probability of being cost-effective at a willingness-to-pay threshold of $125,000 0.5% probability of being cost-effective at a willingness-to-pay threshold of $100,000 Scenario Analysis: Model most sensitive to decreased discount rates and the use of immunosuppression regimens made of generic (rather than brand name) drugs	*"We found that islet cell transplantation is not cost-effective when compared to standard therapy for unstable T1DM. Although it shows large improvements in health outcomes over standard therapy, as anticipated it is also much more costly. These extra costs are not offset by more than proportionate improvements in health outcomes."* (p. 13)

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; T1DM = type 1 diabetes mellitus.

Table 13: Summary of Recommendations in Included Guideline

Recommendations	Strength of Evidence and Recommendations
Diabetes Canada, 2018[3]	
"Individuals with type 1 diabetes with inadequate glycemic control characterized by marked glycemic lability and/or severe hypoglycemia despite best efforts to optimize glycemic control and who have a) preserved renal function or b) who have had a successful kidney transplant may be considered for islet allotransplantation…" (p. S147)	Level of Evidence: 3 Grade of Recommendation: C

Appendix 5: Additional References of Potential Interest

Health Technology Assessment Included in Previous CADTH Report

Xie X, Rich B, Dendukuri N. Islet transplantation in patients with Type 1 Diabetes Mellitus. (Report No. 66). Montreal (QC): Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); 2014 https://muhc.ca/sites/default/files/micro/m-TAU/muhc_tau_2014_66_islet_transplantation.pdf Accessed 2020 Apr 28

Non-Randomized Study – No Comparator

Anazawa T, Saito T, Goto M, et al. Long-term outcomes of clinical transplantation of pancreatic islets with uncontrolled donors after cardiac death: a multicenter experience in Japan. *Transplant Proc*. 2014 Jul-Aug;46(6):1980-1984.
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Clinical Practice Guideline

Clinical guidelines for pancreatic islet transplantation. Vancouver (BC): BC Transplant; 2014.
http://www.transplant.bc.ca/Documents/Health%20Professionals/Clinical%20guidelines/Clinical%20Guidelines%20for%20Pancreatic%20Islet%20Transplantation_01Sept2014_0.pdf
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Health Policy Advisory Committee on Technology. New and emerging health technologies for diabetes. Herston (AU): HealthPACT Secretariat; 2015.
https://www.coaghealthcouncil.gov.au/Portals/0/December%202015_New%20and%20Emerging%20Health%20Technologies%20for%20Diabetes.pdf Accessed 2020 Apr 28