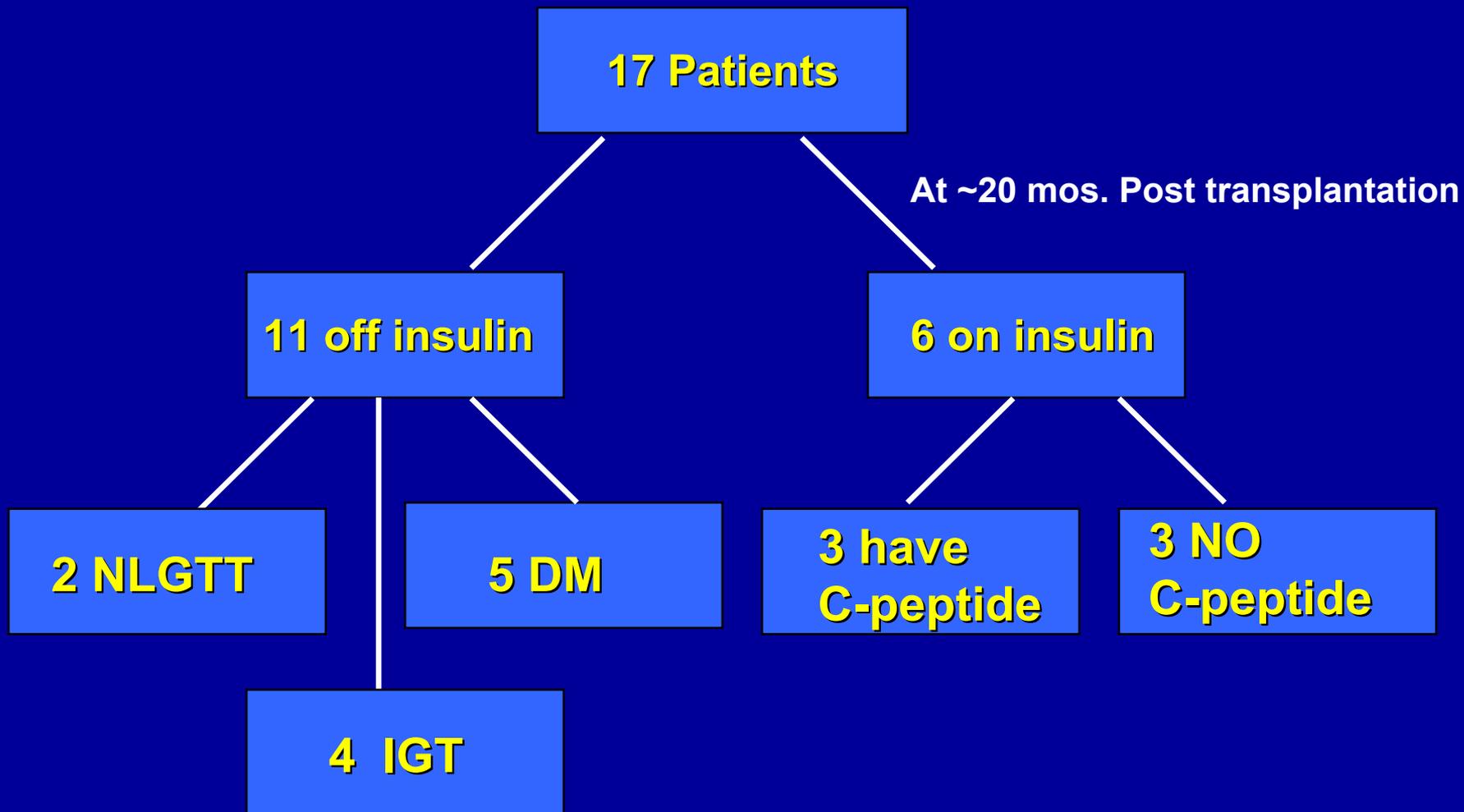


Obstacles and Hurdles Facing the Clinical Application of Islet Transplantation

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ISLET TRANSPLANTATION: THE TURNING POINT THE EDMONTON PROTOCOL

Regan, et al. Diabetes 51:2148, 2002.



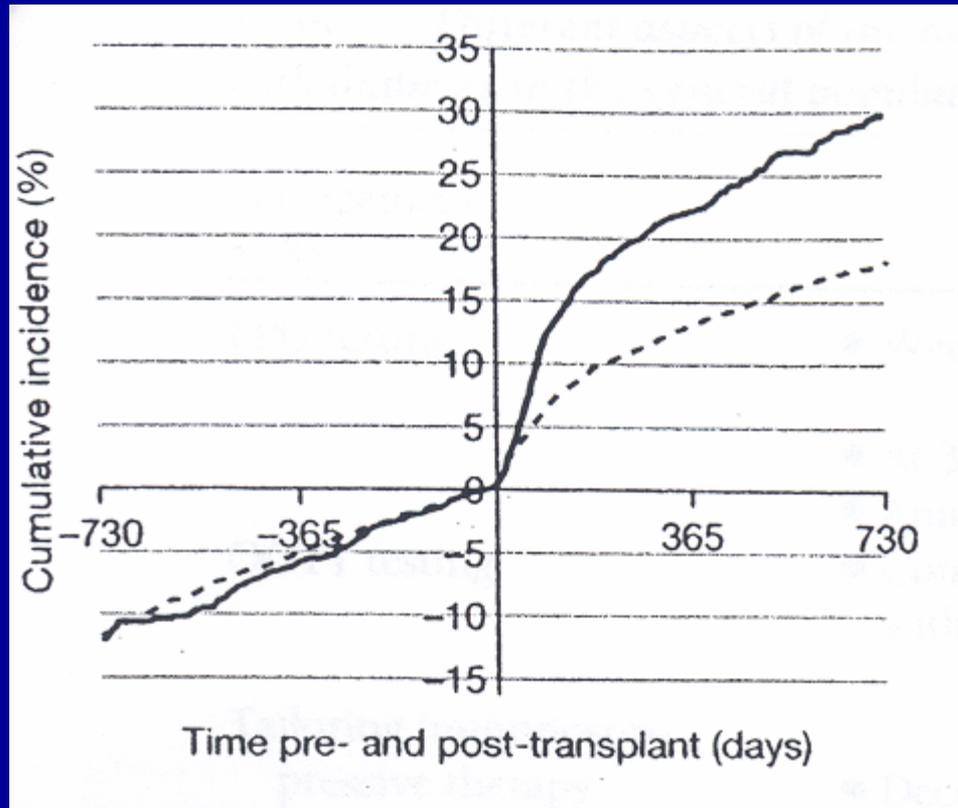
Islet Transplantation in the US Today: Clinical Outcomes

- 1. ~50% of patients become insulin independent 6-12 mos after 2-3 islet grafts. Although considered clinically successful, normal glucose metabolism is **rare****
- 2. At least 1/3 of the insulin independent patients resume insulin therapy within 2 years, but they often require less insulin and are more stable metabolically**
- 3. The majority report improved quality of life, but these studies are uncontrolled and therefore subject to potential bias**
- 4. Little data regarding micro-& macrovascular complications**

What is the Mechanism for the Loss of Beta Cell Function Over Time?

1. Chronic rejection
2. Recurrence of Autoimmunity
3. Immunosuppressive Drugs
 - a. Tacrolimus - Reduces beta cell function.
 - b. Rapamycin - Inhibits mTOR signaling pathway involved in protein synthesis (reduce β -cell proliferation?)
4. Marginal Islet Function/Mass (at best 20-30% NL)
5. Insulin resistance?

Tacrolimus Increases the Incidence of DM After Transplantation



Tacrolimus

Cyclosporine

Davidson, *Diabetes Care*, 2004

Pooled Data for Cultured Islet Transplants at Three Sites

- **n = 75 patients since 2000**
- **74/75 (99%) demonstrated primary function**
- **One-year C-peptide positive: 72/75 (96%)**
- **One-year insulin independence: 64/75 (85%)**

Complications: the Edmonton Experience

Ryan et al, *Diabetes*, 2002

Acute Islet-related Complications

10% bleeding

4% thrombosis

Side effects/drug related complications (n=17)

15 mouth ulcers (sirolimus)

15 increased cholesterol

10 increased BP

10 diarrhea

8 anemia

3 progression of retinopathy

2 nausea/vomiting requiring hydration

2 WBC $< 2 \times 10^9/L$ (sirolimus)

2 (12%) increased creatinine (tacrolimus)

Chronic Islet-related Complications

Fatty liver

FDA Meeting of Biological Response Modifiers Advisory Committee in October, 2003

The Question: What should be the manufacturing requirements and the clinical evidence needed for FDA approval of allogeneic islets as type 1 diabetes treatment?

The Outcome: There are still many basic and clinical questions that need to be resolved. However, some centers have made substantial progress & therefore may ultimately be able to provide sufficient data for FDA approval for islets as a licensed product.

Obstacles & Hurdles to Overcome

1. **Islet Procurement Problems**
2. **Optimization of Islet Production & Culture Methods**
3. **Development of Tests of Islet Viability & Function that Relate to Clinical Outcomes**
4. **Optimization of Immunosuppression Regimens**
5. **Preferred Site for Islet Engraftment?**
6. **Methods to Reduce Implantation Inflammation, Clotting, and Perfusion Deficits**
7. **The Appropriate Clinical Outcome Measures**
8. **Data Needed for Risk-Benefit Assessment for Approval**
9. **Methods to Detect Early Islet Rejection**

Pancreas Allocation Policy: An Obstacle to Islet Transplantation

- 1. The vast majority (>95%) of pancreas organs from obese and older patients (>50 yrs) are not used, yet they are not offered in a timely fashion to the islet transplant community. This is important since cold ischemic time is much more critical for successful islet than whole pancreas transplantation.**
- 2. UNOS kidney-pancreas allocation committee has no representation from either the islet transplant surgeon or the diabetes community.**

Pancreas Allocation Policy: Suggestions

- 1. Limit time (<4 hrs) for offers for pancreas transplantation or provide pancreases directly for islet transplantation from donors with BMI >30 and > 50 yrs.**
- 2. Involve islet transplanters and diabetologists in the pancreas allocation process.**

The Current Clinical Outcome Measures

Insulin Independence = HbA1c < 6.5% off insulin

Thus, insulin independent patients could be classified as prediabetic or diabetic and many are.

Suggestion: Clinical outcomes regarding metabolic status are better defined on basis of ADA criteria of glycemic control , e.g. NGT, IGT, IFG, non-insulin requiring DM

Partial Success = C-peptide secretion & reduced insulin dose

Residual beta cell function has commonly been tested using arginine stimulation or mixed meals rather than glucose stimulated insulin/c-peptide secretion

Clinical Assessment of β -cell Function: A Suggestion

Insulin Independent Patients:

- 1. Oral GTT (with early insulin and C-peptide sampling to better characterize secretion)**
- 2. Stepped glucose infusion \pm Arginine**
- 3. Euglycemic insulin clamp (a measured sensitivity is needed to interpret secretion data)**
- 4. In future an assessment of islet mass**

Clinical Assessment of β -cell Function: A Suggestion

Insulin Requiring Patients:

- 1. Mixed meal**
- 2. Stepped glucose infusion \pm Arginine**
- 3. In future an assessment of islet mass**

Clinical Assessment of Glycemic Control & Hypoglycemia: A Suggestion

- 1. Oral GTT**
 - **24 hr (q1hr) glucose monitoring in the hospital to monitor glucose excursions (MAGE) & hypoglycemia**
- 3. Monthly 8 point profile (Pre & 2h post meal, bedtime, & 3am) glucose meter measurements**
- 4. CGMS for postprandial hyperglycemia & lability**
- 4. Validated Hypoglycemia Scoring System**

Clinical Assessment of Complications: A Suggestion

- 1. Fundus photos**
 - Microalbumin excretion and GFR**
- 3. Sensory testing, nerve conduction, RR interval**
- 4. Endothelial Function Studies**
- 5. Carotid IMT & Coronary Perfusion Studies**
- 6 Measurement of Hypoglycemic Counterregulation
& Awareness**
- 6 Potential complications related to therapy**

What is Needed?

**Multidisciplinary Centers Able to Conduct
State-of the Art Physiological, End Organ,
and Behavioral Outcome Studies on Islet
Graft Recipients (GCRC based)**

The Risk-Benefit Assessment

Benefit: Insulin independence or sufficient C-peptide secretion to make glucose control easier without hypoglycemia.
Better glucose control than is generally achievable
Potential decrease in DM complications

Risks: The acute complications of the procedure, side-effects of the anti-rejection drugs, potential for neoplasia, infections, poor wound healing, pneumonitis

The Risk-Benefit Assessment: Questions That Remain

- 1. Uncertainty about diabetic nephropathy benefit**
- 2. Potential adverse effects on CVD, since transplantation increases risk of CVD, hypertension & hypercholesterolemia**
- 3. Will the duration of islet function be sufficient to have an impact?**

Will Islet Transplantation Prevent or Reverse Diabetic Nephropathy?

Pro: Reversal of mesangial accumulation & BM thickening 10 yrs after successful pancreas transplantation. Robertson, et al NEJM, 2004

Con: 1. Development of renal failure (16.5% in 3 yrs.) in non-kidney graft recipients. Ojo, et al NEJM, 2003

2. 38% decrease in GFR after 1 yr in recipients of bladder drained pancreas transplant alone. Mazur. et al Transplantation, 2004

3. Pancreas transplantation produces better and more sustained glycemic control

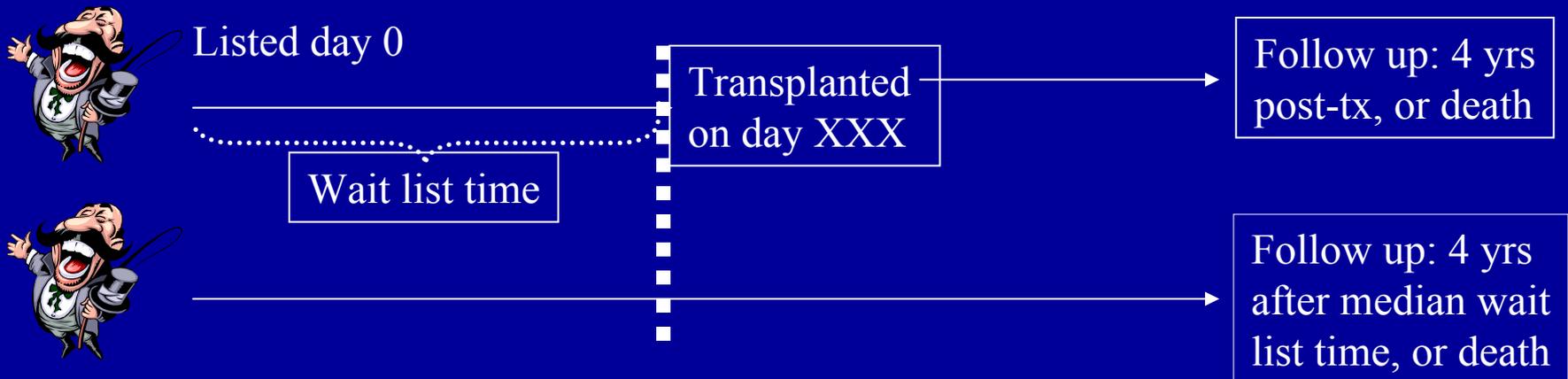
Does Pancreas Transplantation Improve

Mortality?

Harlan, JAMA 2003

Methods:

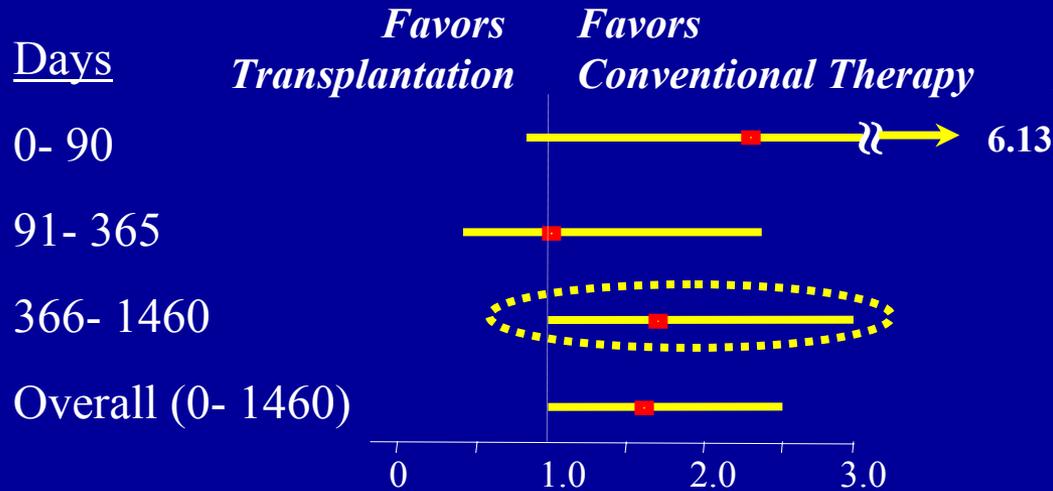
- UNOS national database, 1995 – 2000
- Patients subdivided according to procedure anticipated (PTA, PAK, SPK)
- Social Security Death Master File (SSDMF) searched for ALL patients once listed for a pancreas transplant
- Included ALL deaths (regardless of cause or timing)
- Cox hazard regression model for estimating mortality relative risk.



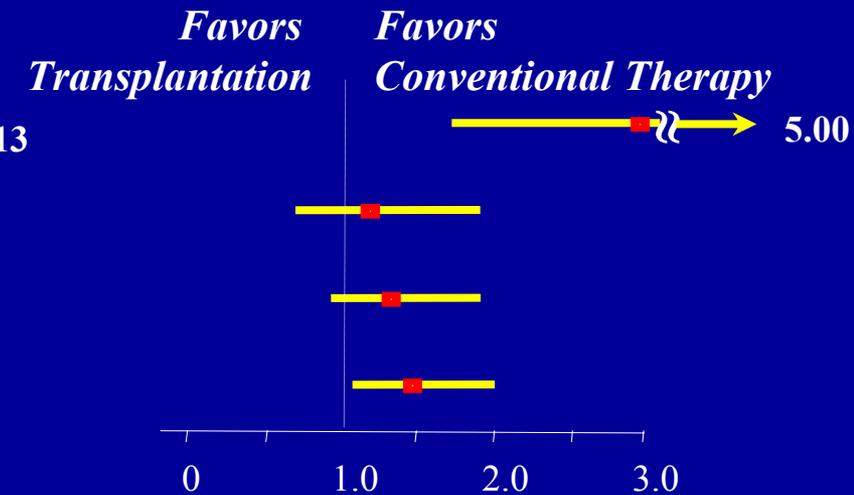
Solitary Pancreas Transplantation and Patient Survival

(Harlan JAMA, 2003).

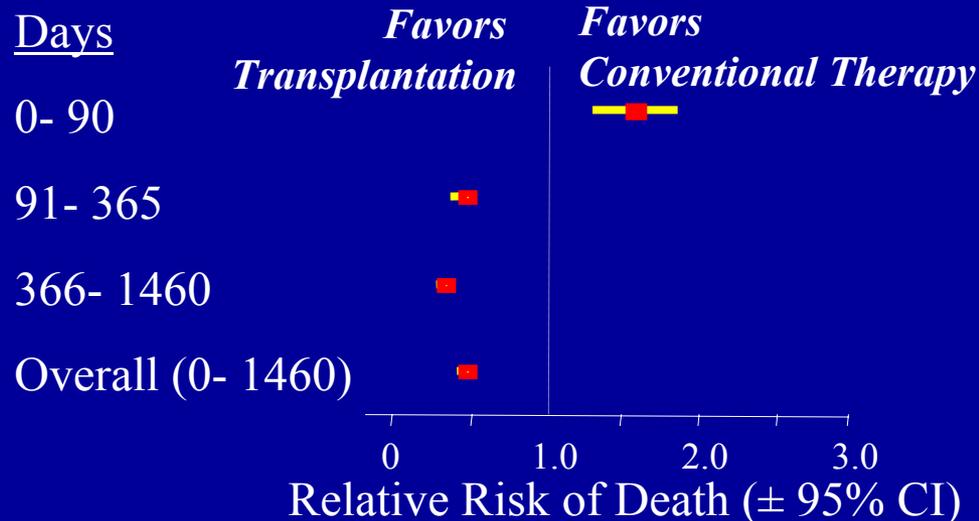
Pancreas-Transplant-Alone (n=672)



Pancreas-After-Kidney (n=1398)



Simultaneous Pancreas-Kidney (n=9502)



Relative Risk of Death (± 95% CI)

Successful Islet Transplantation Scorecard in 2004

Prediction VS ITT

Glycemic Control	Better
Hypoglycemia	Much Better
CNS Function	?
Quality of Life	Better (most)
Retinopathy	Better
Nephropathy	?
Neuropathy	Better
CVD	?
Malignancy	Worse
Survival	?

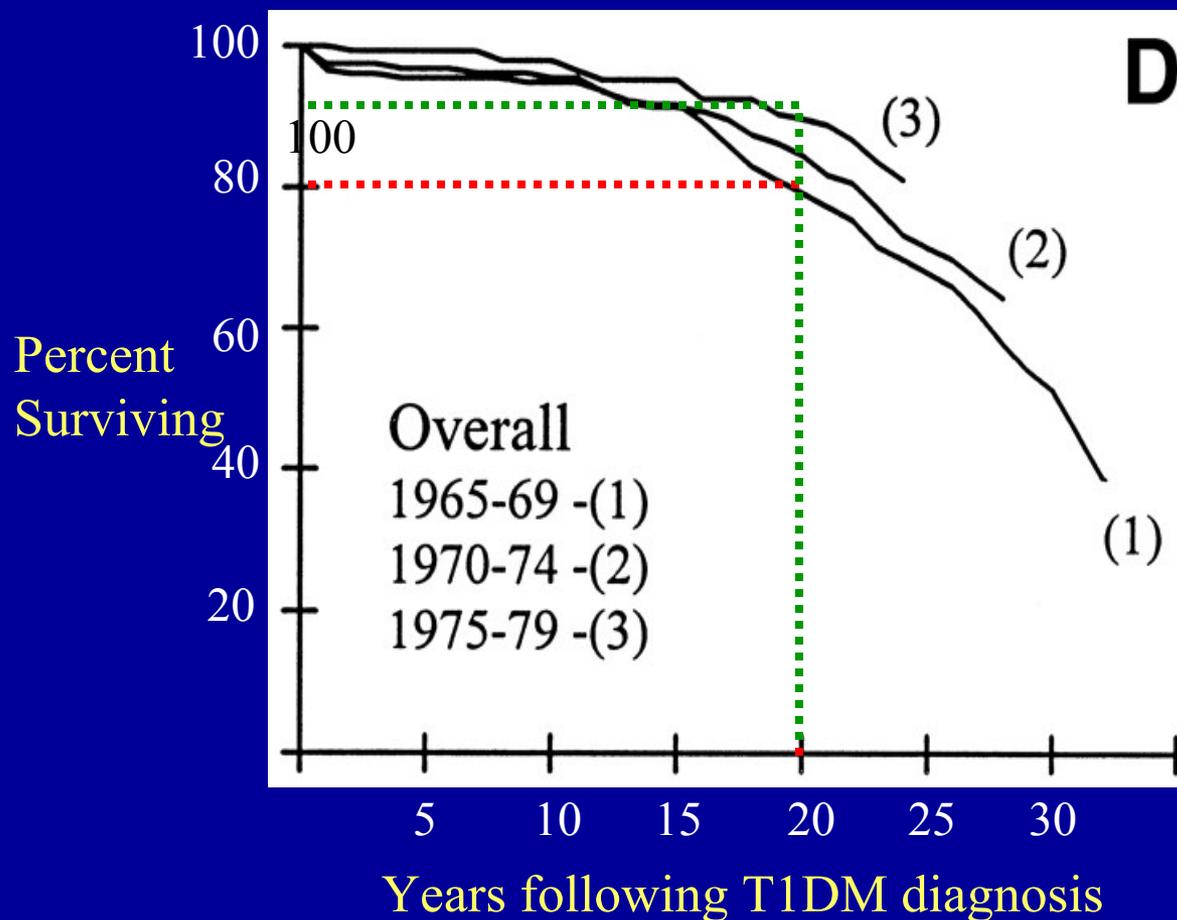
Only 2 Current Indications for Islet Transplantation

- 1. Severe recurrent hypoglycemia & hypoglycemia unawareness**
- 2. Kidney transplant recipient already receiving a steroid-free immunosuppressive regimen**

**Poorly Controlled or Labile T1DM with Rare Exceptions
Should NOT be an Indication Today**

How Good is Standard of Care?

Allegheny County Registry Data: 1075 patients with T1DM



Answer:

Good and improving-

DCCT- 1993

EDIC- 2003

Newer insulins

Insulin delivery systems

Improved glucose monitoring

Importance of BP control

Importance of lipid control

Statins

Improved diets (carb counting)

Preserving islet mass through
early intensive insulin Rx

The Problem of Severe Hypoglycemia: Is It Important Enough to Warrant Islet Tx?

**It's More Common than Appreciated Because Sympathoadrenal Responses & Cognitive Awareness are Markedly Reduced
& 50% of Events Occur during Sleep**

Fear of Hypoglycemia > Fear of Complications



Decreased Commitment to Treatment

- Patients**
- Family Members**
- Physicians**

Severe Hypoglycemia: An Indication for Islet Transplantation

Patients with severe recurrent hypoglycemia and hypoglycemia unawareness that fail to respond to modern MDI or insulin pump therapy delivered by a team of diabetes specialists for 6-12 months.

Severe hypoglycemia and unawareness **must be documented by:**

- A. History (coma, hospitalization, help by another) of events at least 2 times/yr
- B. Glucose meter readings
- C. Hypoglycemia clamp studies

**Why is a Long Clinical Observation Period Needed?
Improved Insulin Management that Reduces Iatrogenic Hypoglycemia May Improve Counterregulation**

What is an Acceptable Outcome?

	Insulin Independent	Insulin Requiring C-peptide Positive
Severe Hypoglycemia	+	+
Islet after Kidney	+	+
Impaired Renal Function	?	-
Poor DM Control	?	?

What Kind of Trials are Needed?

	Duration	Type of Study
Severe Hypoglycemia	1-2 yr	Observational
Islet after Kidney	2-3 yr	Historical Controls
Poor DM Control	5 yr	DCCT type Randomized Controlled Trial