



Fondation
CENTAURE



Inserm



Stratégie de greffe chez le patient diabétique de type 1

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Case report 1

- Female 42 years old
- Type 1 diabetes
- Diabetes duration: 24 years
- Hb A1C 8.5% Insulin therapy: Implantable pump
- Hypoglycemia: once a day, no severe hypoglycemia
- Diabetes complication: neuropathy, retinopathy, nephropathy
- GFR : 44 ml/mn/1.73m² (CKD EPI)
- Blood Group: AB
- No evidence for macroangiopathy

Case report 1: which transplantation ?

- Pancreas transplantation ?
- Islet transplantation ?
- Simultaneous pancreas kidney transplantation ?
- Simultaneous islet kidney transplantation ?
- Kidney transplantation followed by pancreas after kidney ?
- Kidney transplantation followed by islet after kidney ?
- No transplantation, optimal insulin therapy and nephroprotection ?

Case report 2

- Female 27 years old
- Type 1 diabetes
- Diabetes duration: 18 years
- Hb A1C 10.5% Insulin therapy: Lantus 24 UI/day
- Hypoglycemia: 3/weeks, no severe hypoglycemia
- Diabetes complication: neuropathy, retinopathy, nephropathy
- Hemodialysis for 4 years
- Blood Group: AB
- No evidence for macroangiopathy
- Anti HLA antibodies: PRA class I 70%

Case report 2: which transplantation ?

- Pancreas transplantation ?
- Islet transplantation ?
- Simultaneous pancreas kidney transplantation ?
- Simultaneous islet kidney transplantation ?
- Kidney transplantation followed by pancreas after kidney ?
- Kidney transplantation followed by islet after kidney ?

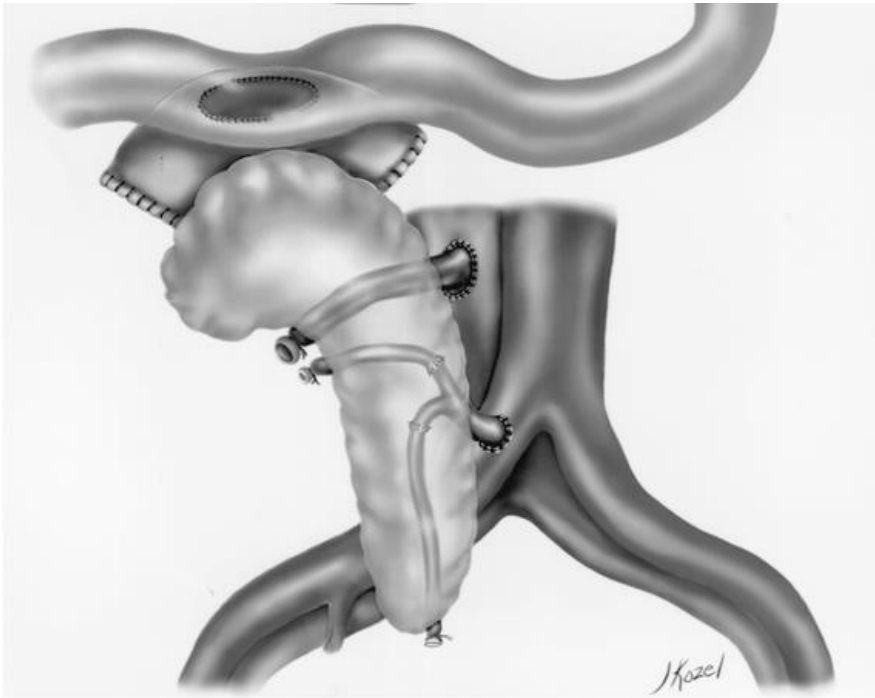
Plan

- Indications et procédures
- Survie du patient et du greffon
- Impact sur le diabète et ses complications
- Immunosuppression
- Stratégie de greffe chez le patient diabétique de type 1

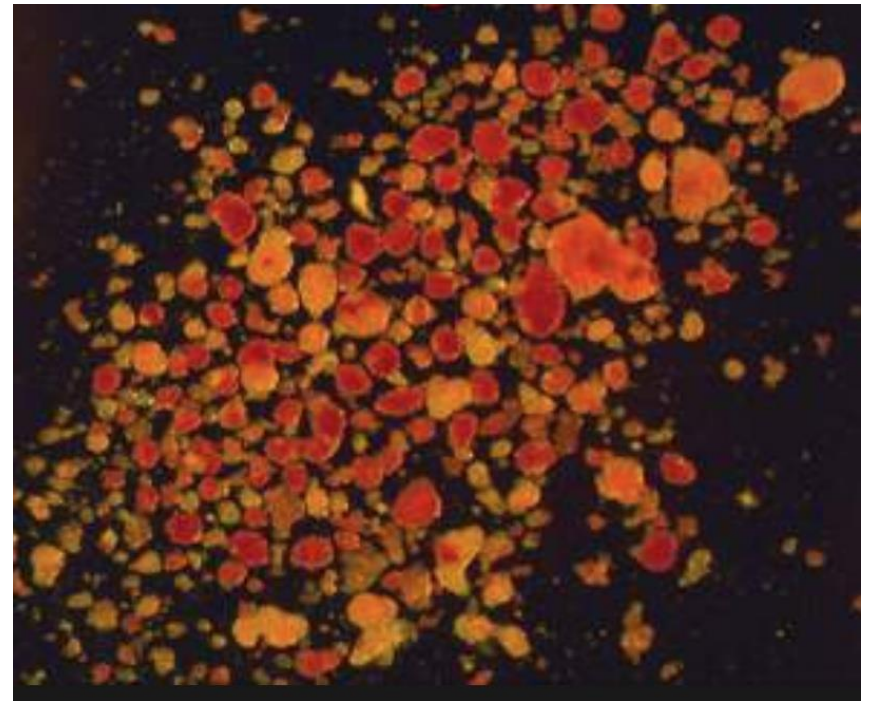
Plan

- **Indications et procédures**
- Survie du patient et du greffon
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β cell replacement for T1D patients



Pancreas transplantation

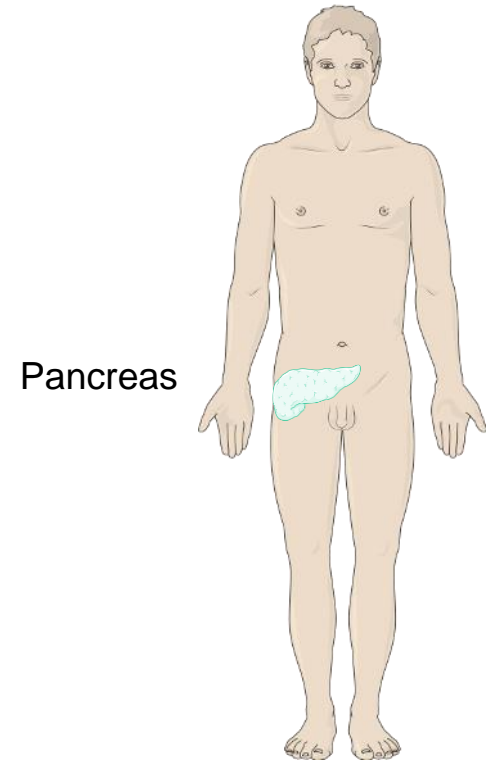
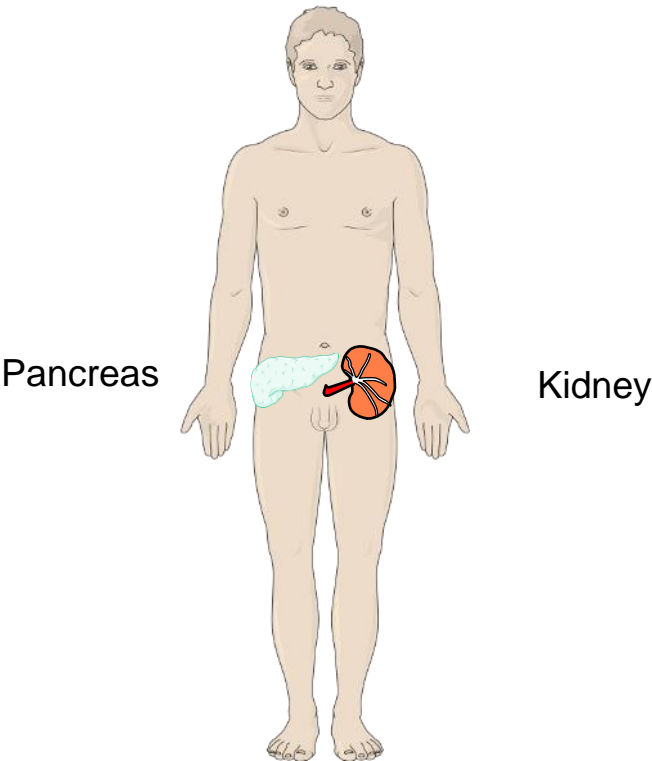


Langerhans Islets

β cell replacement for T1D patients

Simultaneous
pancreas and kidney transplantation

Pancreas transplant alone



T1D patients in ESRD

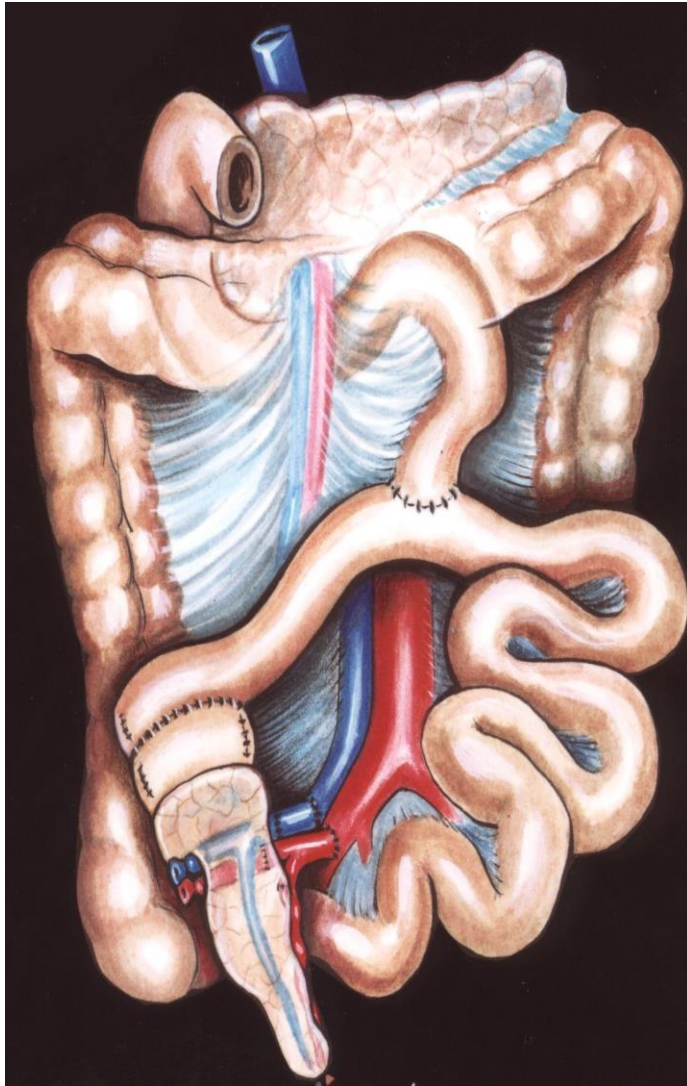
Unstable T1D patients
Brittle diabetes

Activité de greffe de pancréas en France

	2015	2016	2017	2018	2019	2020
Créteil Henri Mondor (AP-HP) (A)	2	2	0	0	0	0
Le Kremlin Bicêtre - Villejuif Paul Brousse (AP-HP) (A)	10	10	14	10	16	12
Lyon (HCL) (A)	25	22	26	21	32	7
Montpellier La Peyronie (A)	8	6	8	3	3	2
Nantes (A)	15	30	20	23	17	8
Paris Saint-Louis (AP-HP) (A)	5	5	7	5	3	0
Toulouse Rangueil (A)	13	14	21	15	13	5
France	78	89	96	77	84	34

Venous and enteric drainage

S
Y
S
T
E
M
I
C



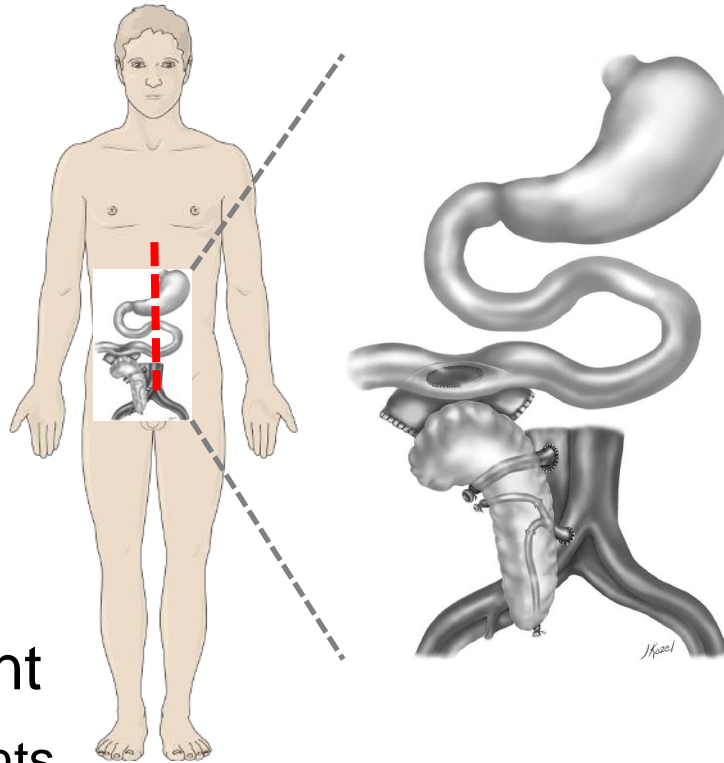
Enteric drainage

Roux-en-Y loop

Latero-lateral loop

β cell replacement for T1D patients

Pancreas transplantation - a major operation



Recipient
T1D patients

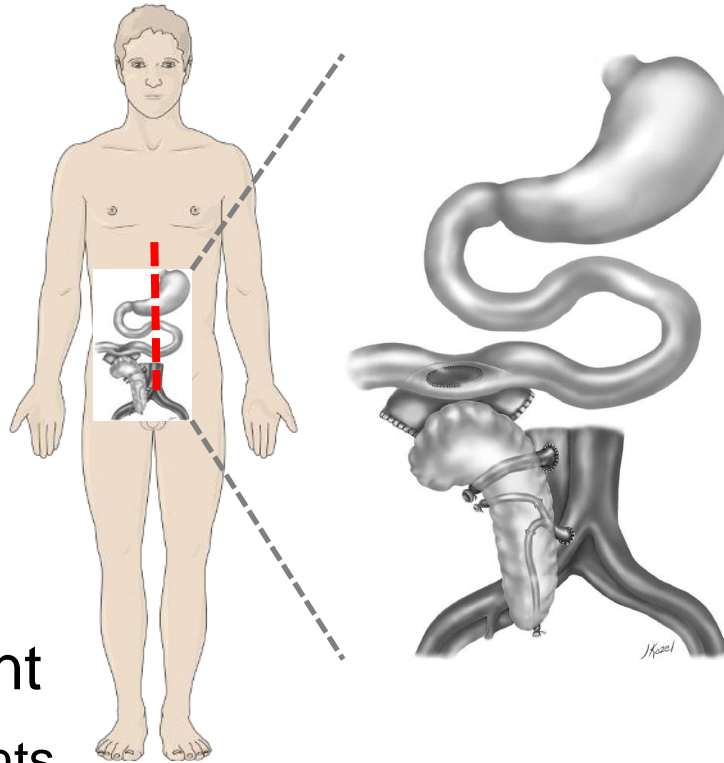
High incidence of
post-operative complications

- Leakage
- Hemorrhage
- Thrombus of pancreas.....

Une DIVA !!!

β cell replacement for T1D patients

Pancreas transplantation - a major operation



Recipient
T1D patients

High incidence of
post-operative complications

- Leakage
- Hemorrhage
- Thrombus of pancreas.....

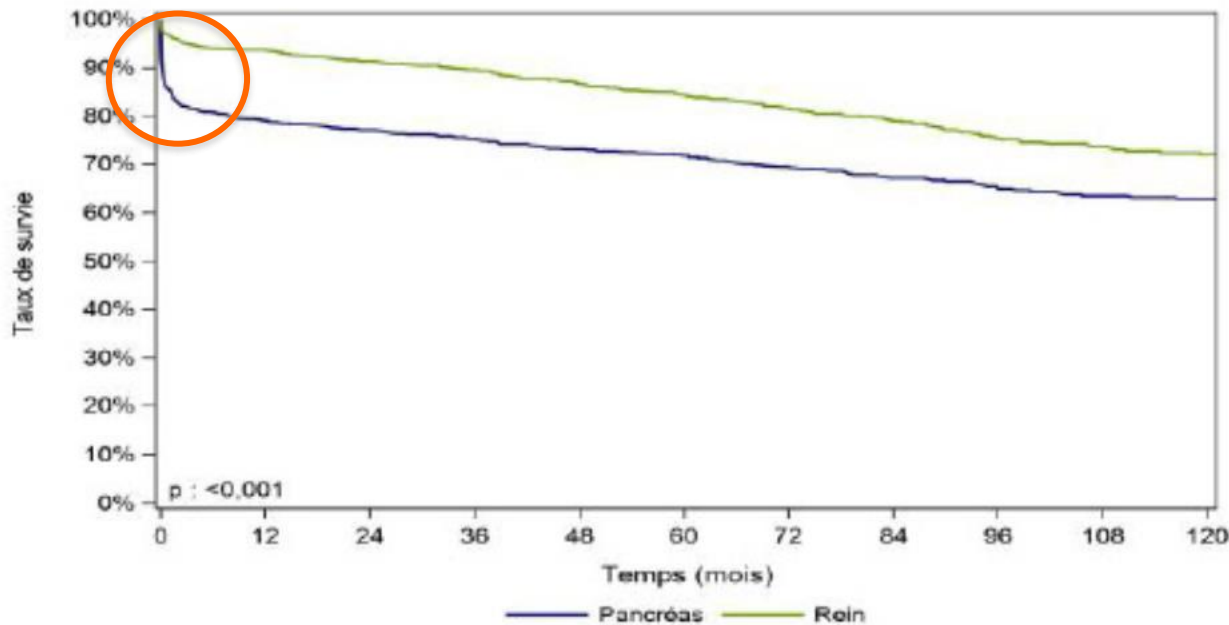
Une DIVA !!!

Post-operative pancreas graft loss: 10-15%

Secondary surgery for thrombosis, hemorrhage, fistula, abscess: 30%

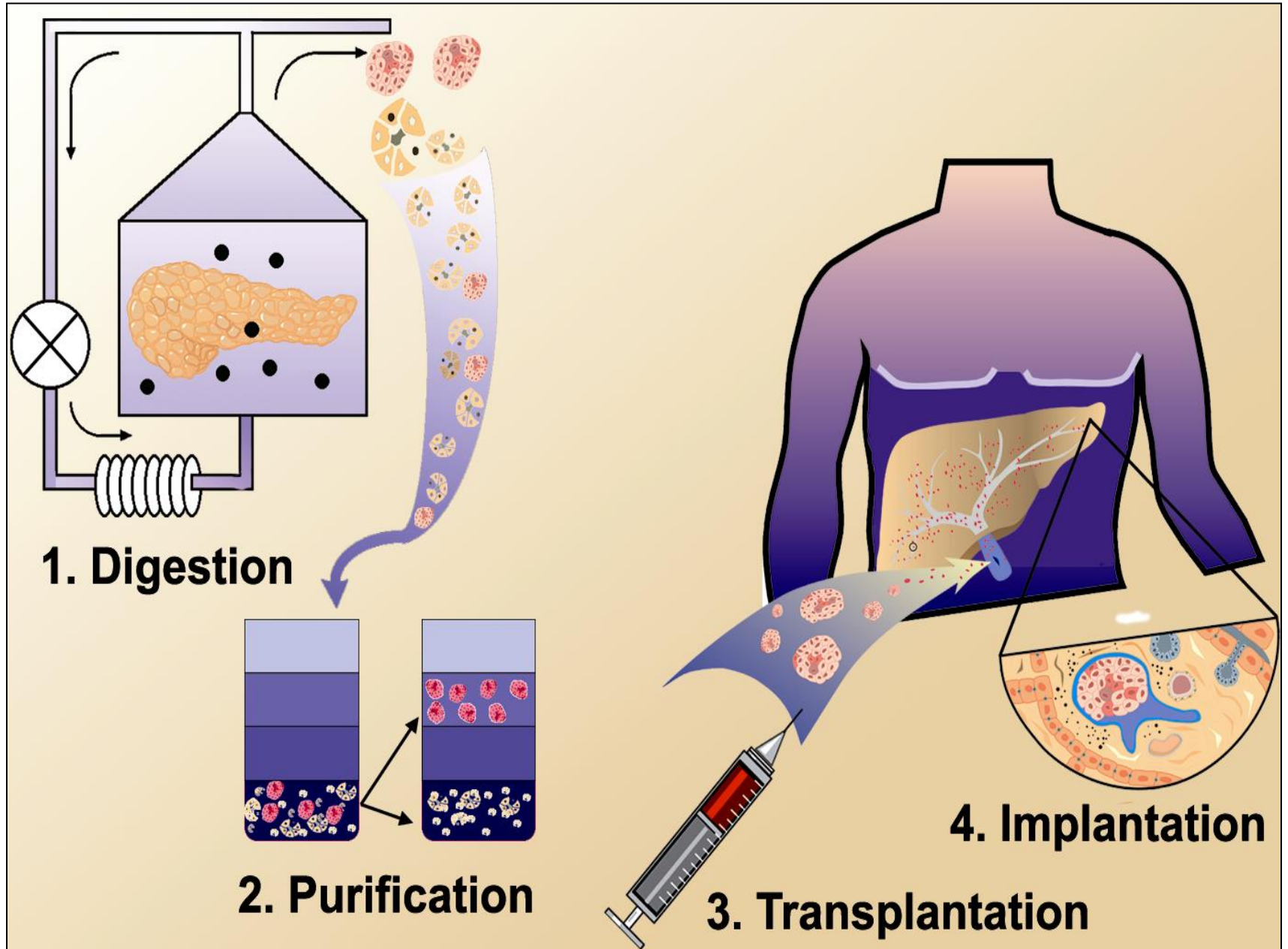
Early technical failures and graft losses

Simultaneous pancreas and kidney transplantation



Graft thrombosis or graft removal because of bleeding, anastomotic leaks, pancreatitis, and/or infection.

Islet graft





Dissection du pancréas



Labo cGMP



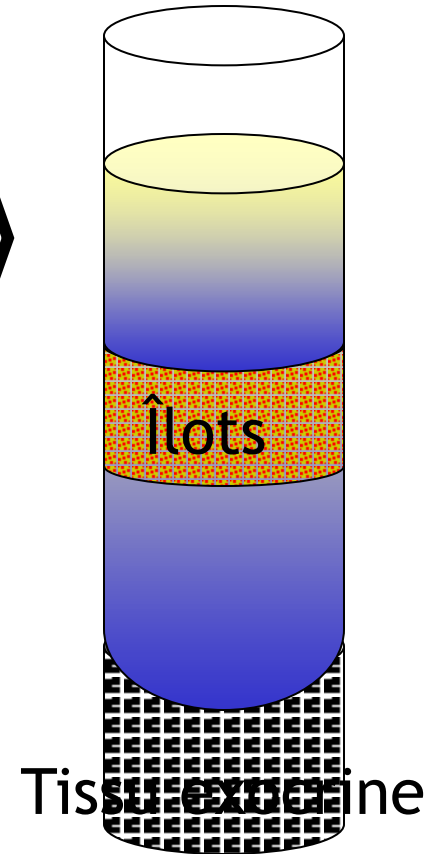
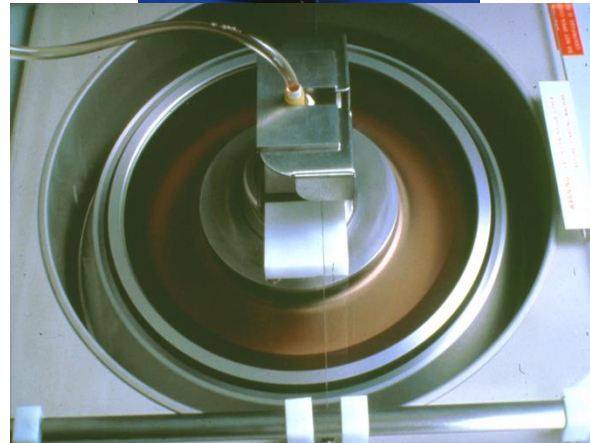
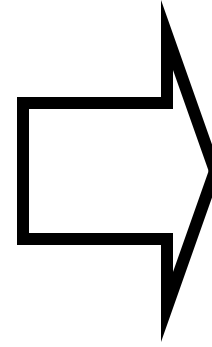
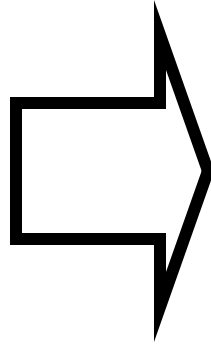
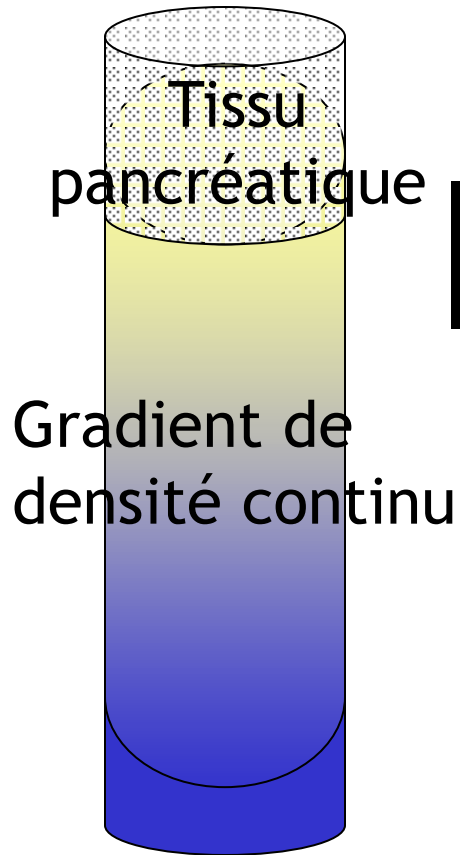
Injection intraductale de collagénase

Circuit de digestion - chambre de Ricordi




Méthode de purification

Centrifugation sur COBE 2991



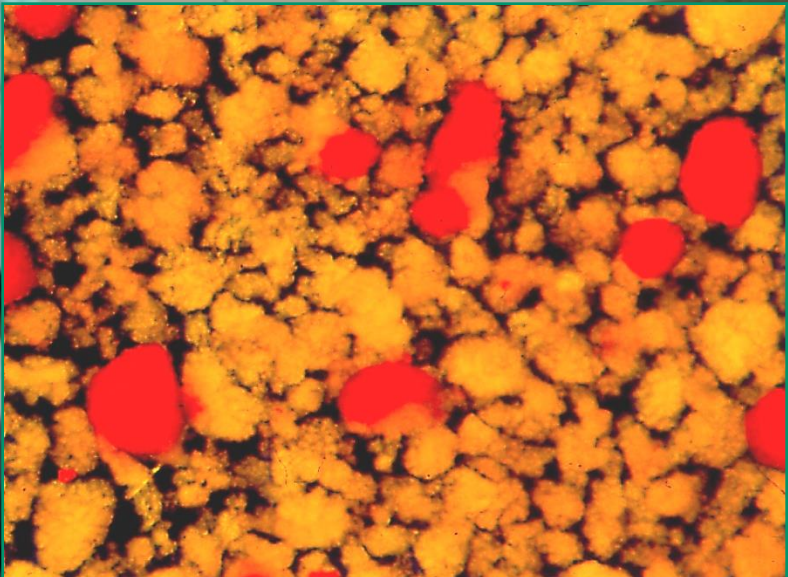


Multi-Well-Plate
Task 1



1. Preparation of the multi-well plate
2. Addition of the cell suspension
3. Incubation of the cells
4. Addition of the substrate
5. Measurement of the cell growth

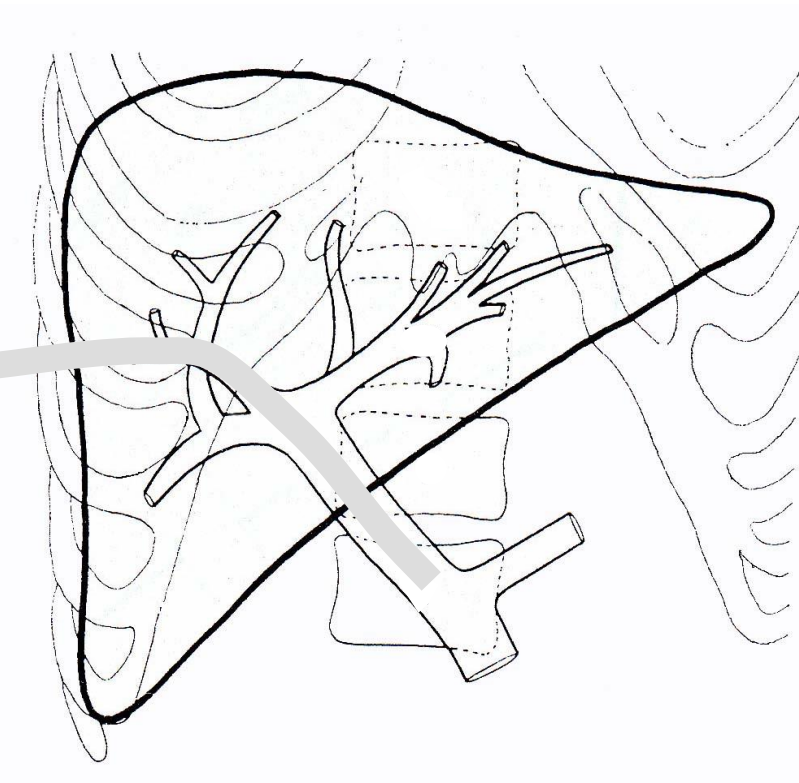
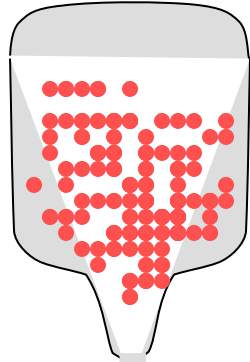
1. Preparation of the multi-well plate
2. Addition of the cell suspension
3. Incubation of the cells
4. Addition of the substrate
5. Measurement of the cell growth



Le greffon

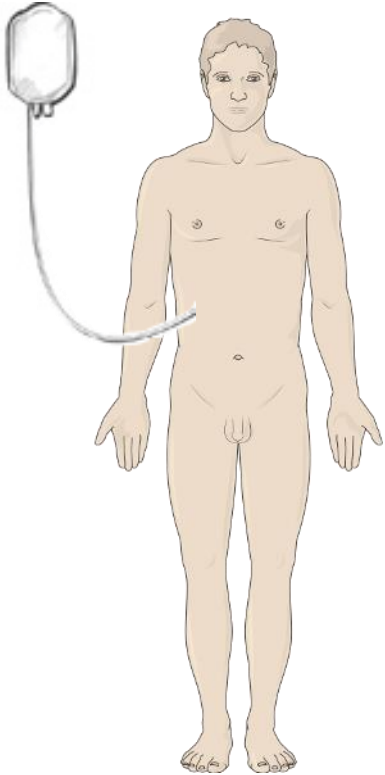


Infusion intraportale

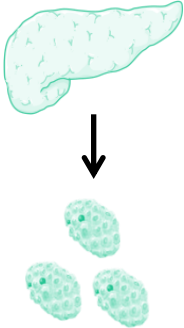


β cell replacement for T1D patients: islet transplantation

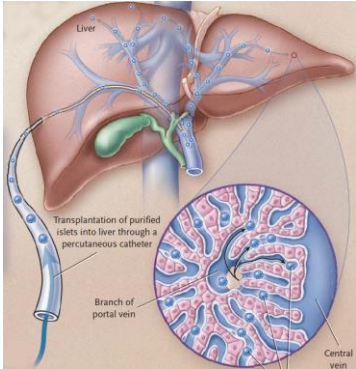
Islet transplant alone



Unstable T1D patients
Brittle diabetes

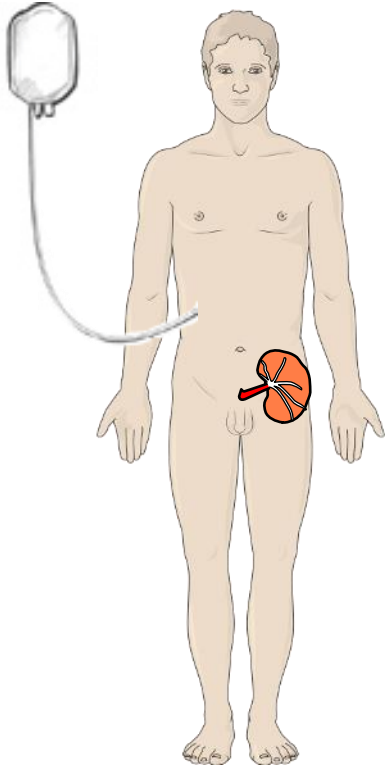


Islets



2-3 Islet preparations
per patient

Islet after kidney transplantation



Kidney

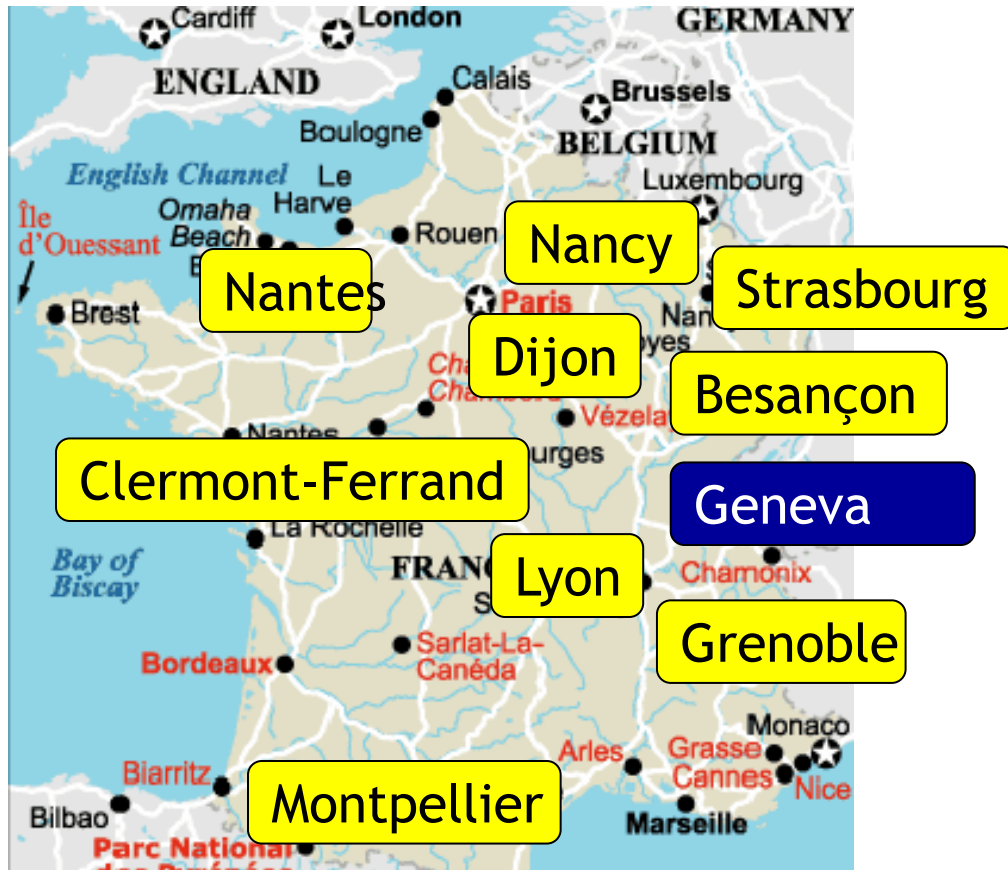
T1D patients in ESRD

Tableau IL8. Activité des laboratoires d'isolement d'îlots de Langerhans (source : rapport d'activité d'isolement d'îlots de Langerhans à partir de 2015)

Laboratoire	Année	Visée Clinique			
		Nombre de Pancréas organes reçus	Pancréas envoyé en anatomopathologie sans isolement	Isolement ayant abouti à une greffe	Echec d'isolement
Genève	2015	35	0	17	18
Genève	2016	27	0	10	17
Genève	2017	41	3	25	13
Genève	2018	30	0	20	10
Genève	2019	30	0	17	13
Genève	2020	12	0	9	3
Grenoble	2015	1	0	0	1
Grenoble	2016	5	0	0	5
Grenoble	2017	5	1	0	4
Grenoble	2018	1	0	0	1
Grenoble	2019	0	.	.	.
Lille	2015	40	0	9	31
Lille	2016	46	0	12	34
Lille	2017	45	0	7	38
Lille	2018	25	1	6	18
Lille	2019	13	0	3	10
Lille	2020	3	0	0	3
Montpellier	2015	0	.	.	.
Montpellier	2016	0	.	.	.
Montpellier	2017	0	.	.	.
Montpellier	2018	1	0	0	1
Montpellier	2019	1	0	0	1
Montpellier	2020	0	.	.	.
Paris Saint-Louis	2015	10	0	3	7
Paris Saint-Louis	2016	12	0	2	10
Paris Saint-Louis	2017	14	0	3	11
Paris Saint-Louis	2018	13	0	2	11
Paris Saint-Louis	2019	16	0	3	13
Paris Saint-Louis	2020	7	0	1	6
Total	2015	86	0	29	57
Total	2016	90	0	24	66
Total	2017	105	4	35	66
Total	2018	70	1	28	41

Islet Isolation in France/Geneva

The GRAGIL Network



- ✓ 1992: Geneva program
- ✓ 1997: GRAGIL network
- ✓ 1999: First patient in France

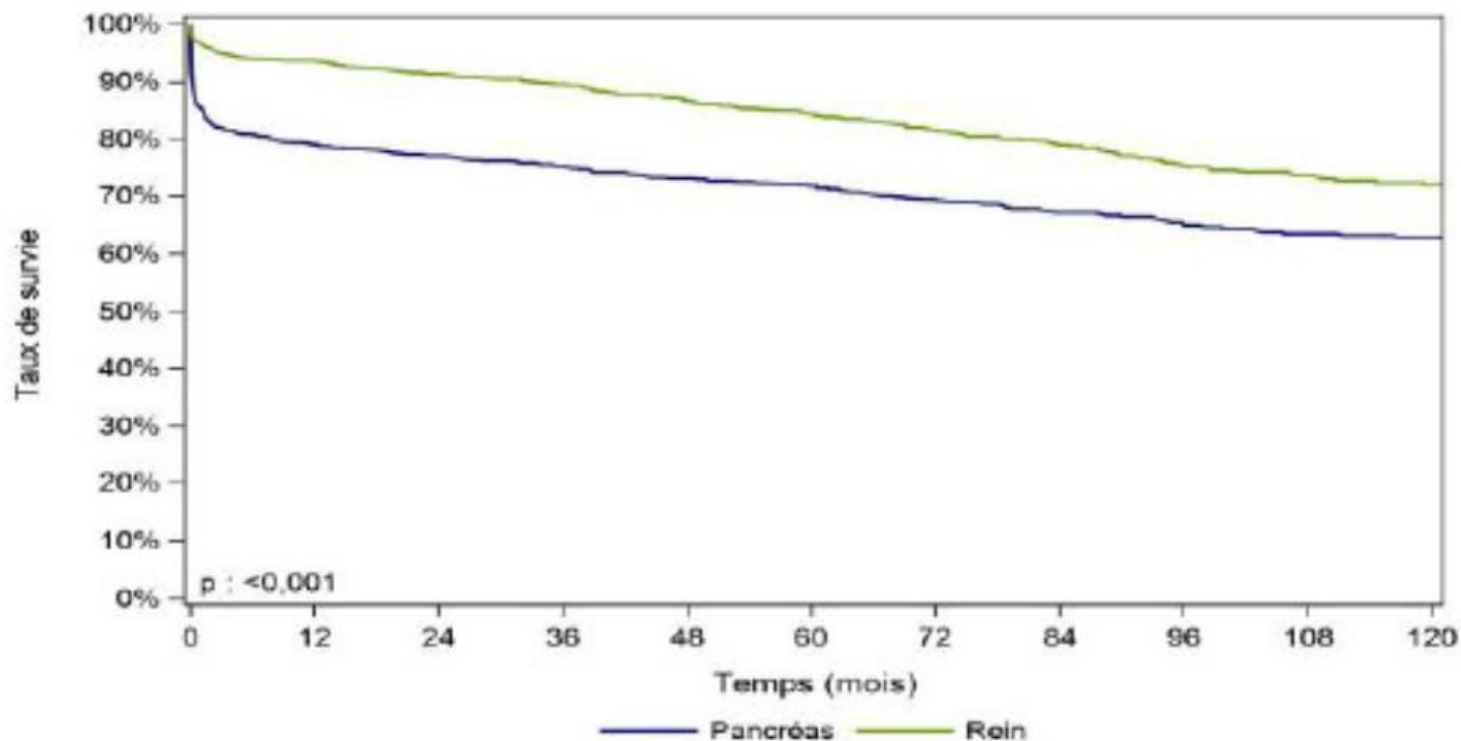
- ✓ 272 islet transplantations
- ✓ 157 patients

Berney et al. Curr Opin Organ Transplant 2004; 9: 72.
Kempf et al. Transplantation 2005; 79: 1200.

Plan

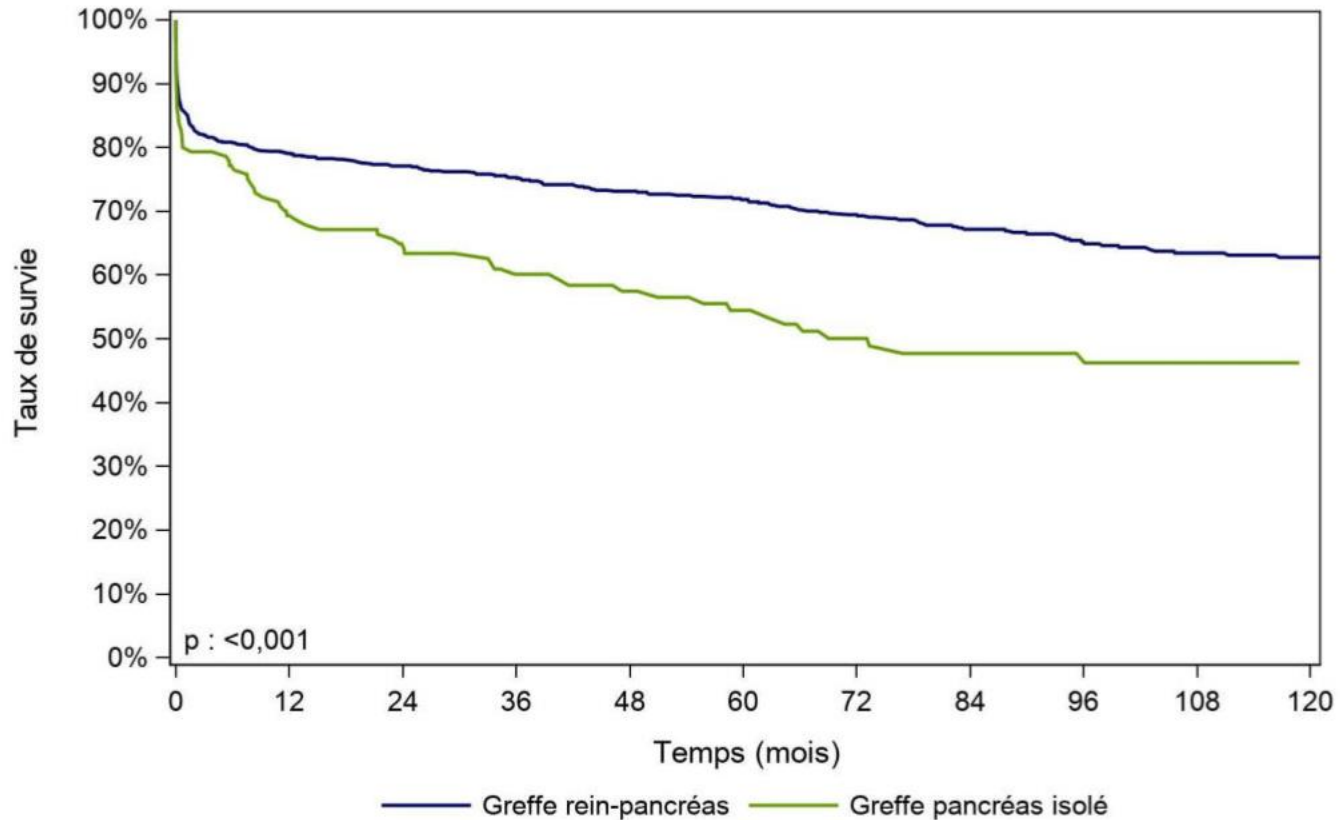
- Indications et procédures
- **Survie du patient et du greffon**
- Impact sur le diabète
- Immunosuppression
- Suivie des patients
- Stratégie de greffe chez le patient diabétique de type 1

Pancreas and kidney survival in simultaneous pancreas and kidney transplantation

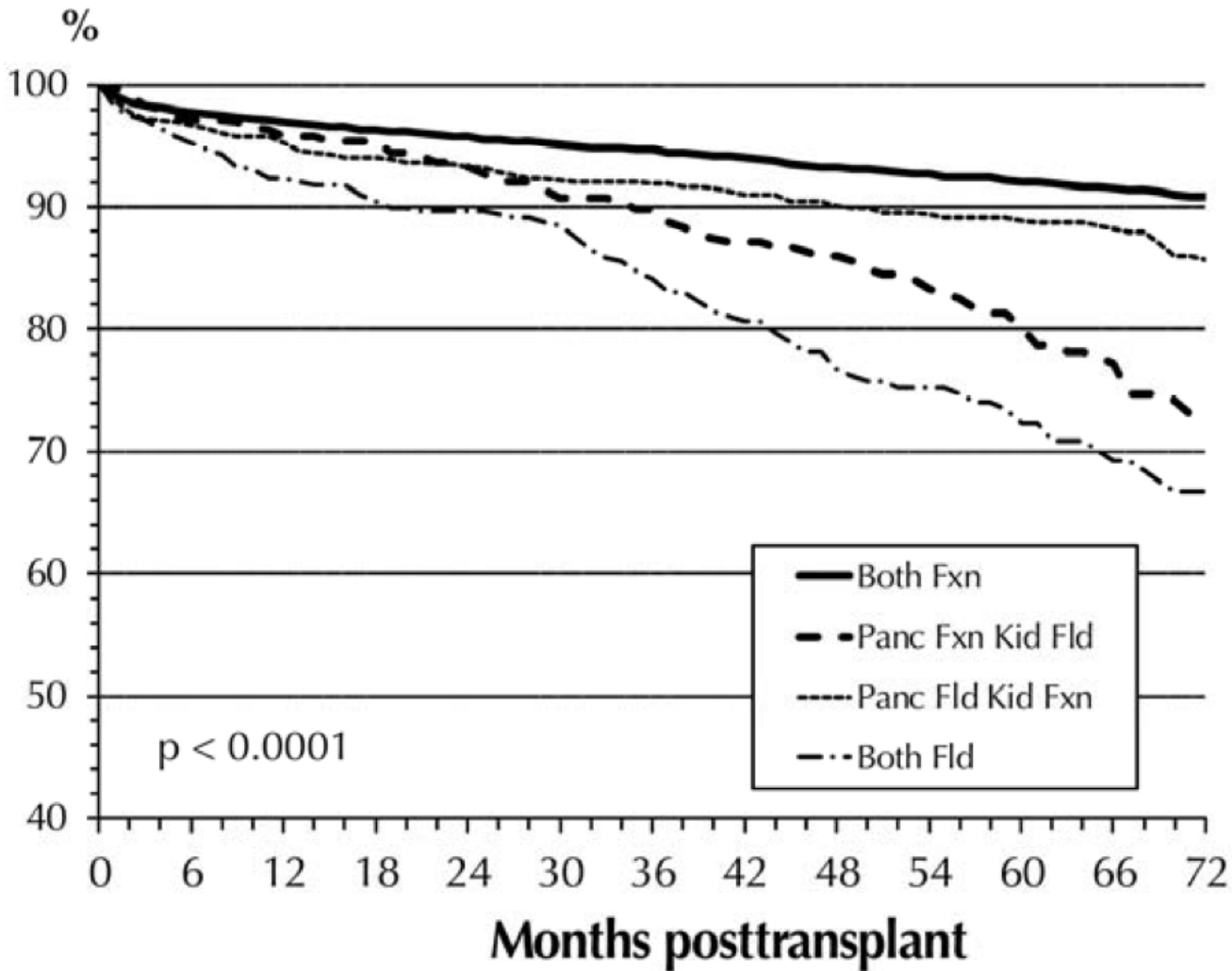


Survie du pancréas: SPK versus PTA

Figure PA4. Survie du greffon pancréatique selon type de greffe pancréatique (2007-2019)



SPK patient survival by pancreas and kidney graft status



10-years Islet graft survival Gragil Network

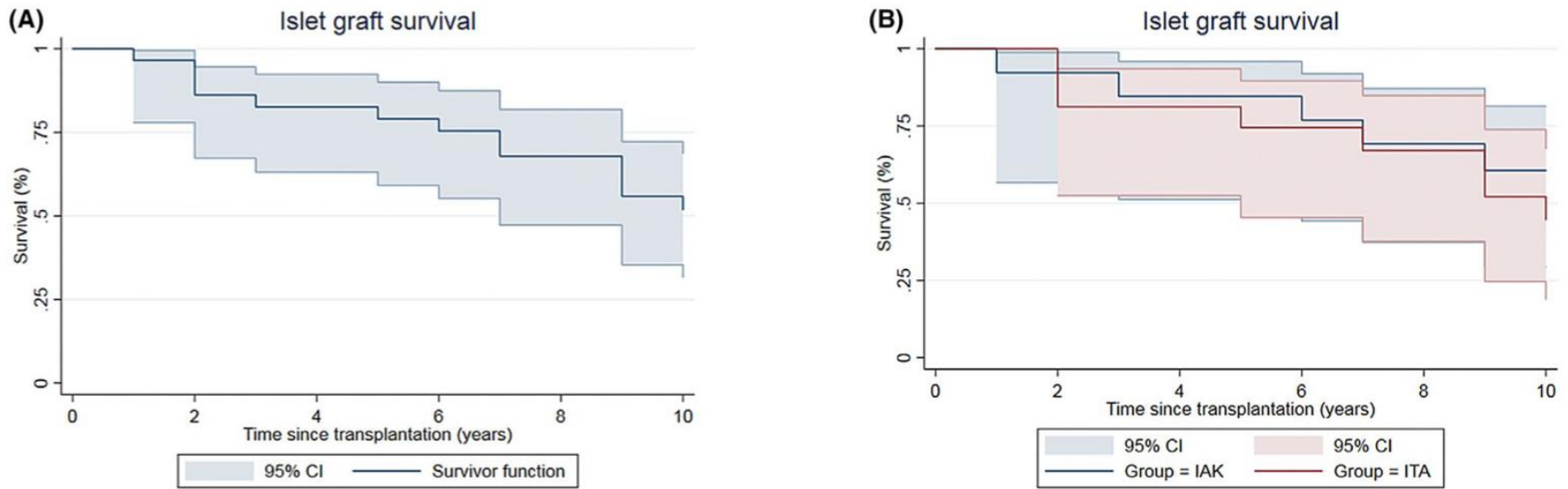


FIGURE 3 (A) Islet graft survival over follow-up in the global population, (B) ITA and IAK recipients [Color figure can be viewed at wileyonlinelibrary.com]

Plan

- Indications
- Survie du patient et du greffon
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 - Transplantation de pancréas
 - Greffe d'îlots
- Immunosuppression
- Stratégie de greffe chez le patient diabétique de type 1

Metabolic follow-up after long-term pancreas graft survival

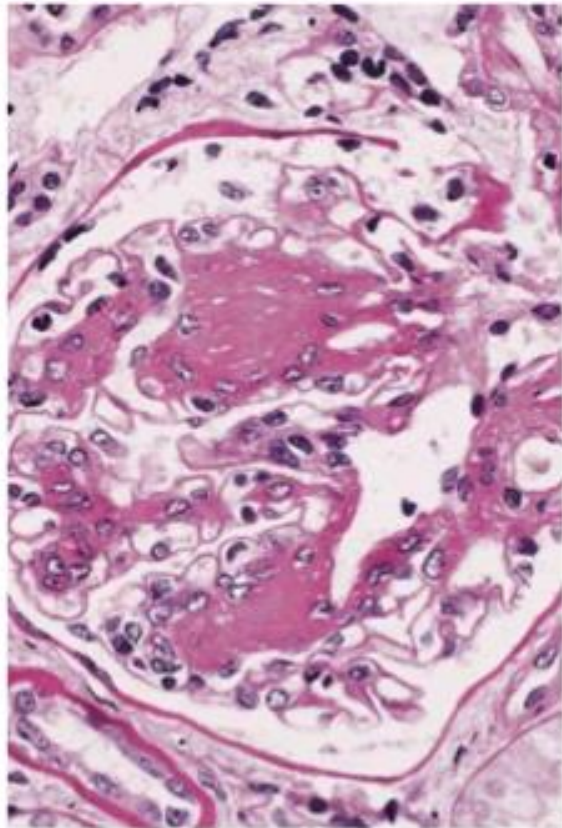
Table 2 Parameters of pancreas and kidney graft function from 3 months to 10 years after simultaneous pancreas/kidney transplantation.

	3 months (n=38)	1 year (n=38)	3 years (n=38)	5 years (n=38)	10 years (n=38)	P
Fasting blood glucose (mg/dl)	78±2	81±2	82±2	84±2	91±2	<0.01 ^{a,b,c,d,e}
HbA _{1c} (%)	4.6±0.1	4.9±0.1	4.9±0.1	5.0±0.1	5.3±0.2	<0.001 ^{f,a,b,d,g,h}
120 min glucose (mg/dl)	118±7	122±9	110±9	118±9	150±13	<0.05 ^{d,g,i}
Normal glucose tolerance (%)	67	56	68	66	37	<0.05 ^{b,g,i}
BMI (kg/m ²)	21.1±0.4	21.9±0.5	22.4±0.5	22.8±0.5	23.5±0.7	<0.05 ^{j,a,b,c,d,g}
Fasting insulin (μU/ml)	21±2	23±2	18±1	18±1	16±1	<0.05 ^d
AUC _{insulin} (μU/ml×min)	11 735±1365	11 754±985	11 215±886	11 801±995	11 772±1074	Ns
Incremental insulin ΔI ₃₀ /ΔG ₃₀ (μU/ml)	221±50	176±28	157±28	157±22	168±36	Ns
HOMA-IR	4.1±0.4	4.5±0.5	3.7±0.3	3.7±0.3	3.5±0.3	Ns
Matsuda-deFronzo ISI	3.6±0.4	2.9±0.2	3.5±0.3	3.1±0.2	3.2±0.3	Ns
S-creatinine	1.3±0.1	1.3±0.1	1.4±0.1	1.5±0.1	1.5±0.1	Ns

Mean ± S.E.M. ANOVA with repeated measurements.

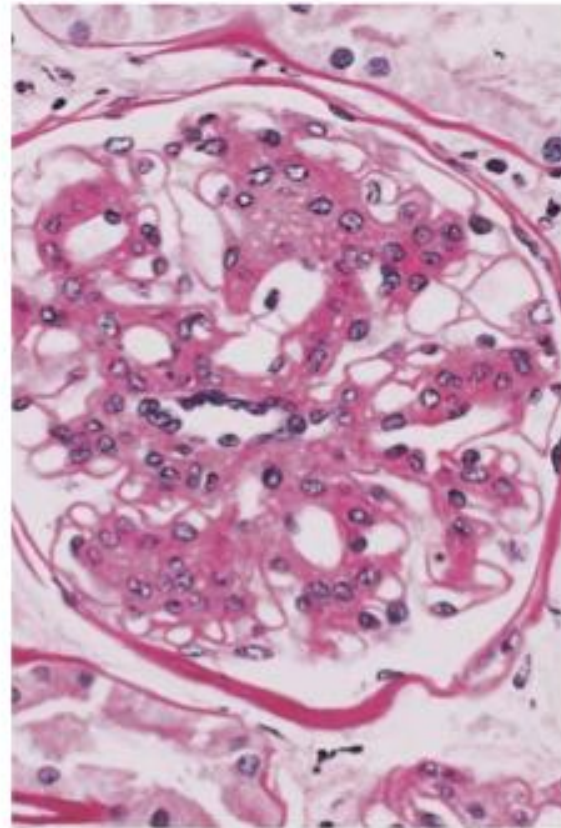
^a3 months versus 5 years. ^b3 months versus 10 years. ^c1 year versus 5 years. ^d1 year versus 10 years. ^e1 year versus 3 years. ^f3 months versus 1 year. ^g3 years versus 10 years. ^h3 years versus 5 years. ⁱ5 years versus 10 years. ^j3 months versus 3 years.

La transplantation du pancréas corrige les lésions de néphropathie diabétique



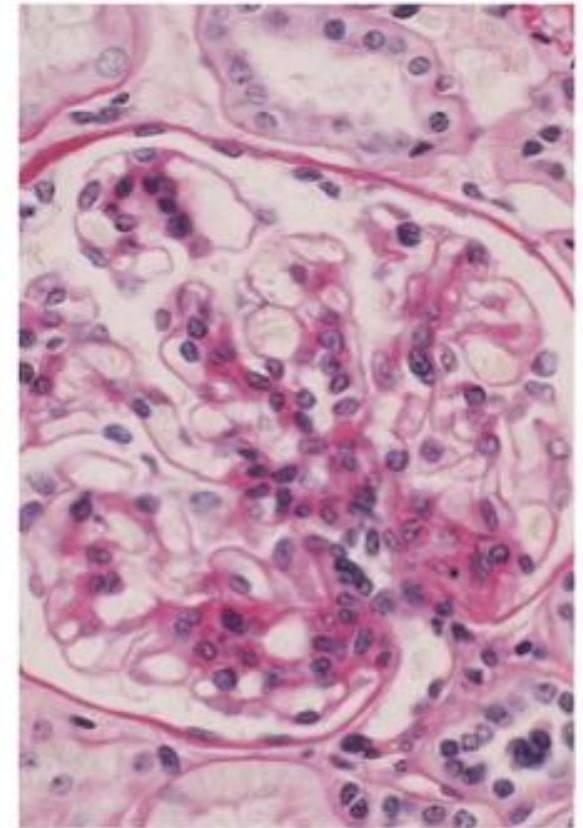
A

Avant



B

5 ans



C

10 ans

Intérêt de la transplantation rein et pancréas chez le diabétique de type 1 en IRT

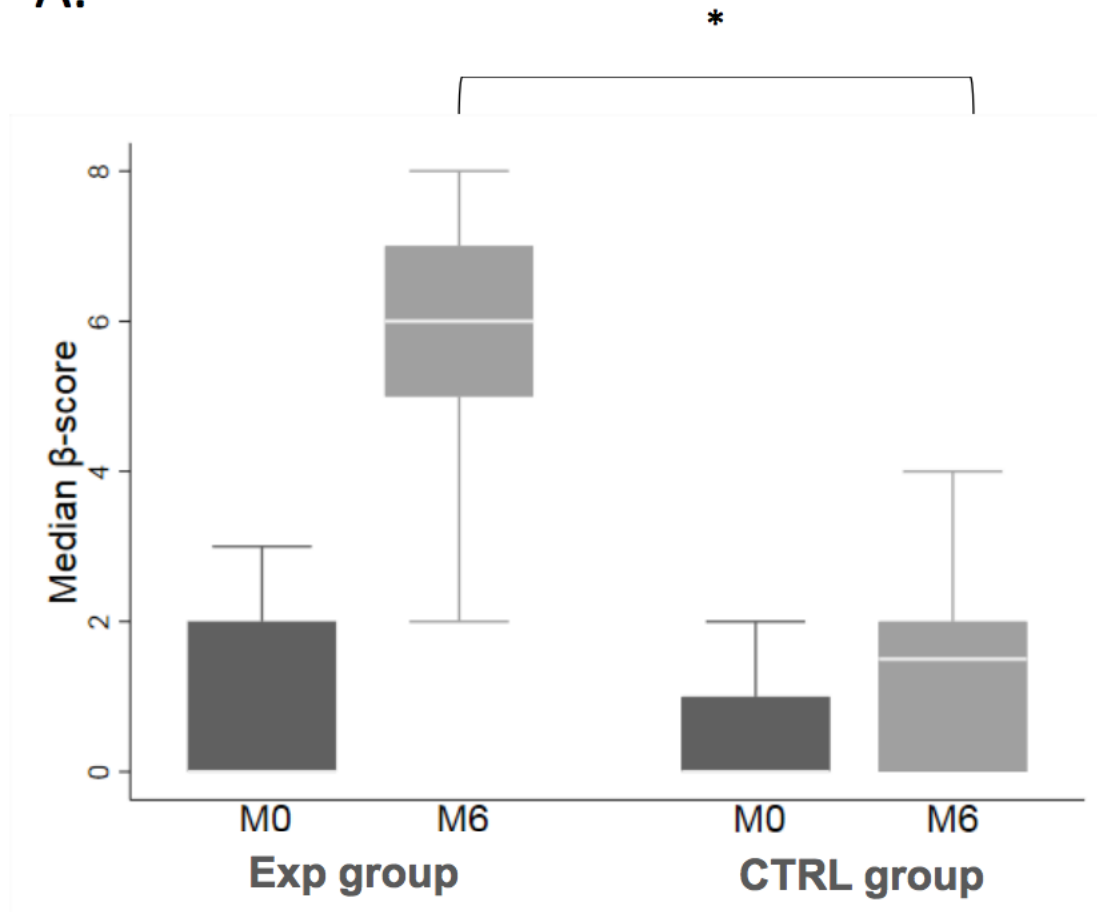
- **Amélioration de la survie du patient (vs R seul et dialyse)**
- **Stabilisation ou amélioration des complications dégénératives**
 - **Microangiopathie**
 - **Rénales:**
 - amélioration des lésions préexistantes
 - prévention de la récurrence sur le greffon
 - **Neurologiques périphériques:**
 - amélioration après 2 ans
 - augmentation de la vitesse de conduction nerveuse motrice et sensitive
 - **Ophthalmologiques**
 - stabilisation
 - amélioration après plusieurs mois si peu évolutive
 - **Macro-angiopathie coronaire et carotidienne**
 - **Amélioration de la qualité de vie**

Plan

- Indications
- Survie du patient et du greffon
- **Impact sur le diabète et ses complications**
 - Transplantation de pancréas
 - **Greffe d'îlots**
- Immunosuppression
- Stratégie de greffe chez le patient diabétique de type 1

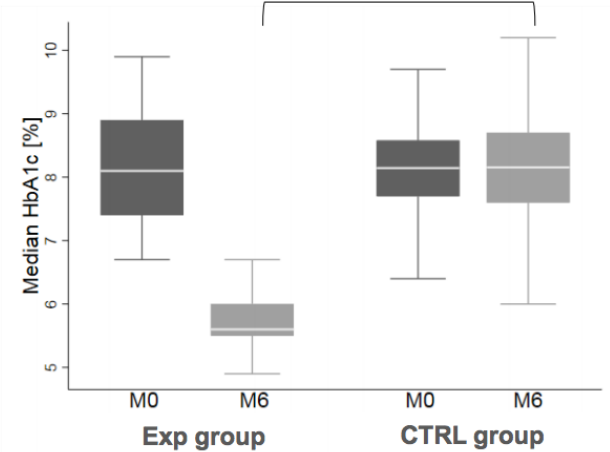
Assessing Islet transplantation compared to insulin therapy in type 1 diabetes: a randomized parallel study

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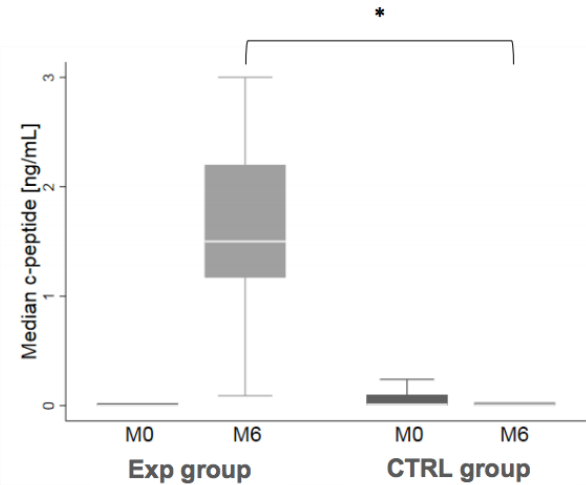


Assessing Islet transplantation compared to insulin therapy in type 1 diabetes: a randomized parallel study

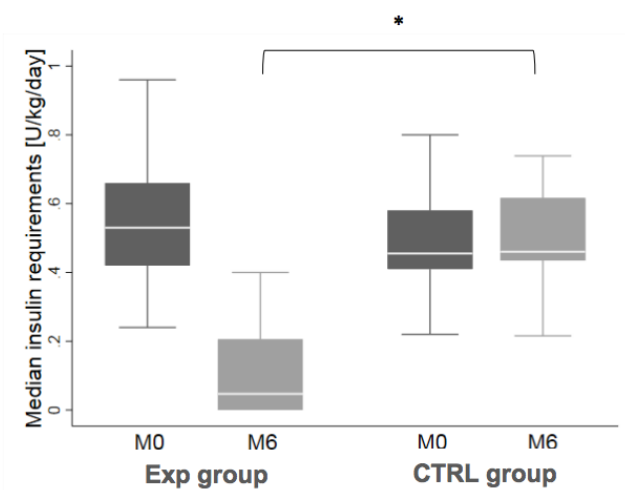
A.



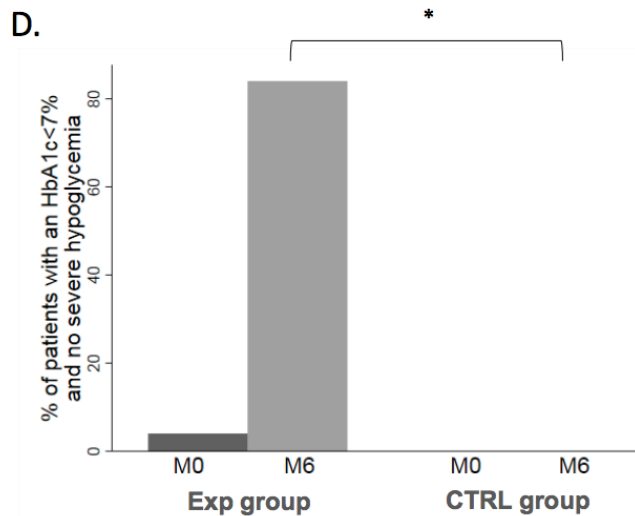
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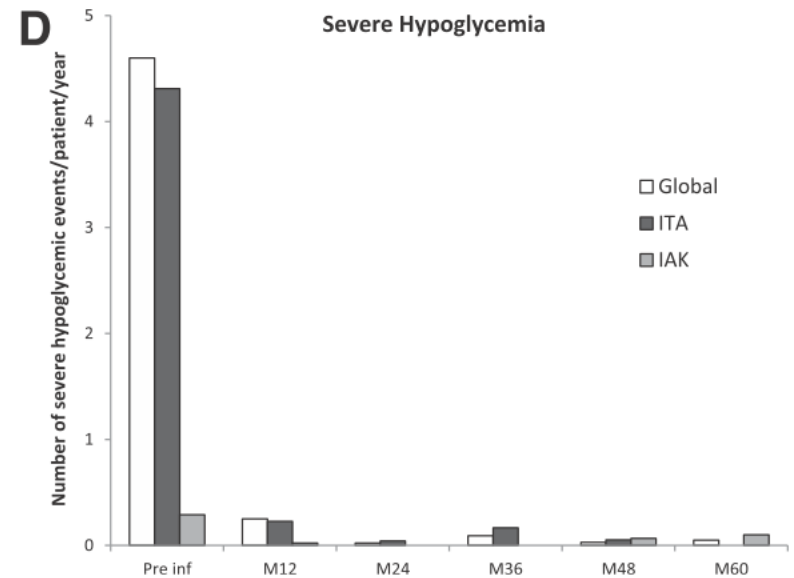
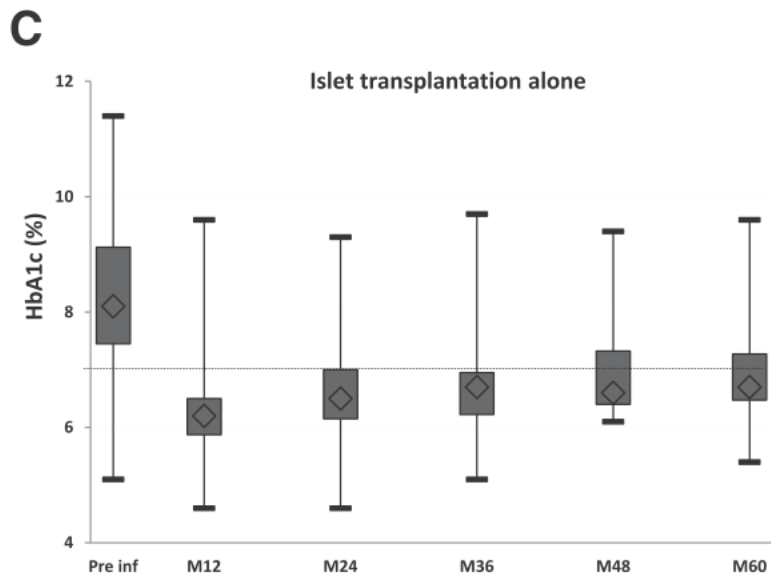
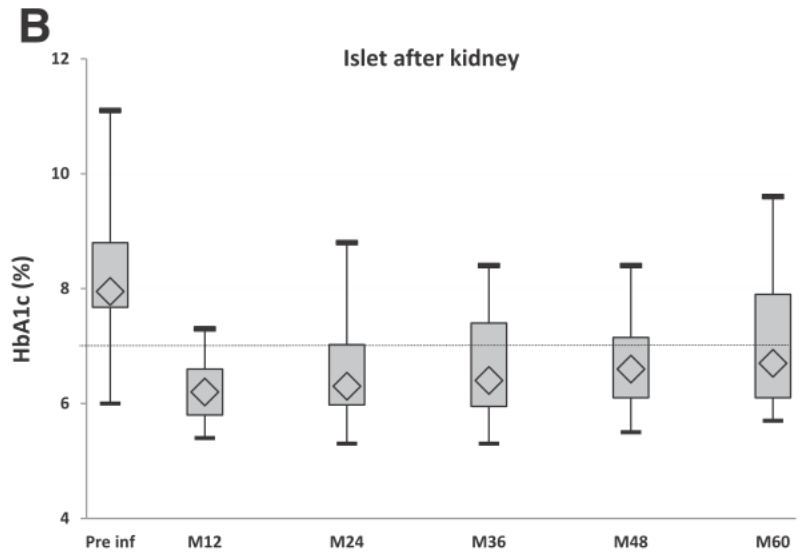
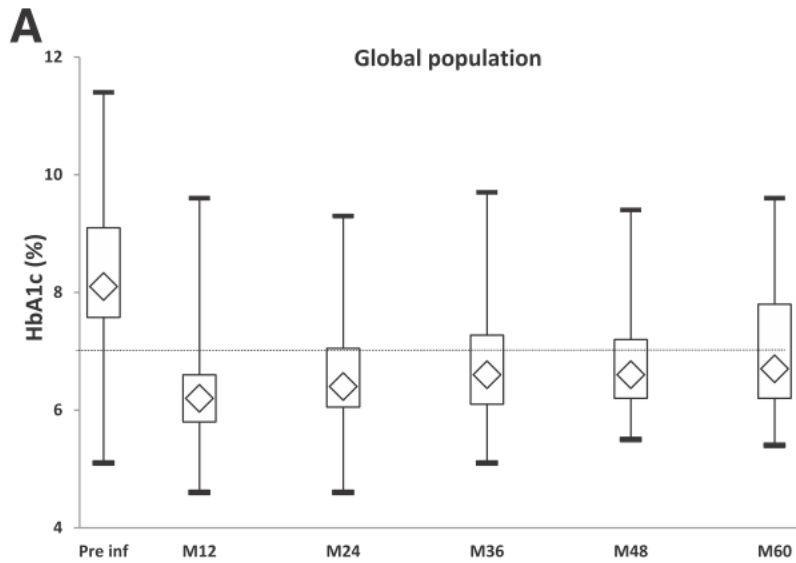


C.



D.





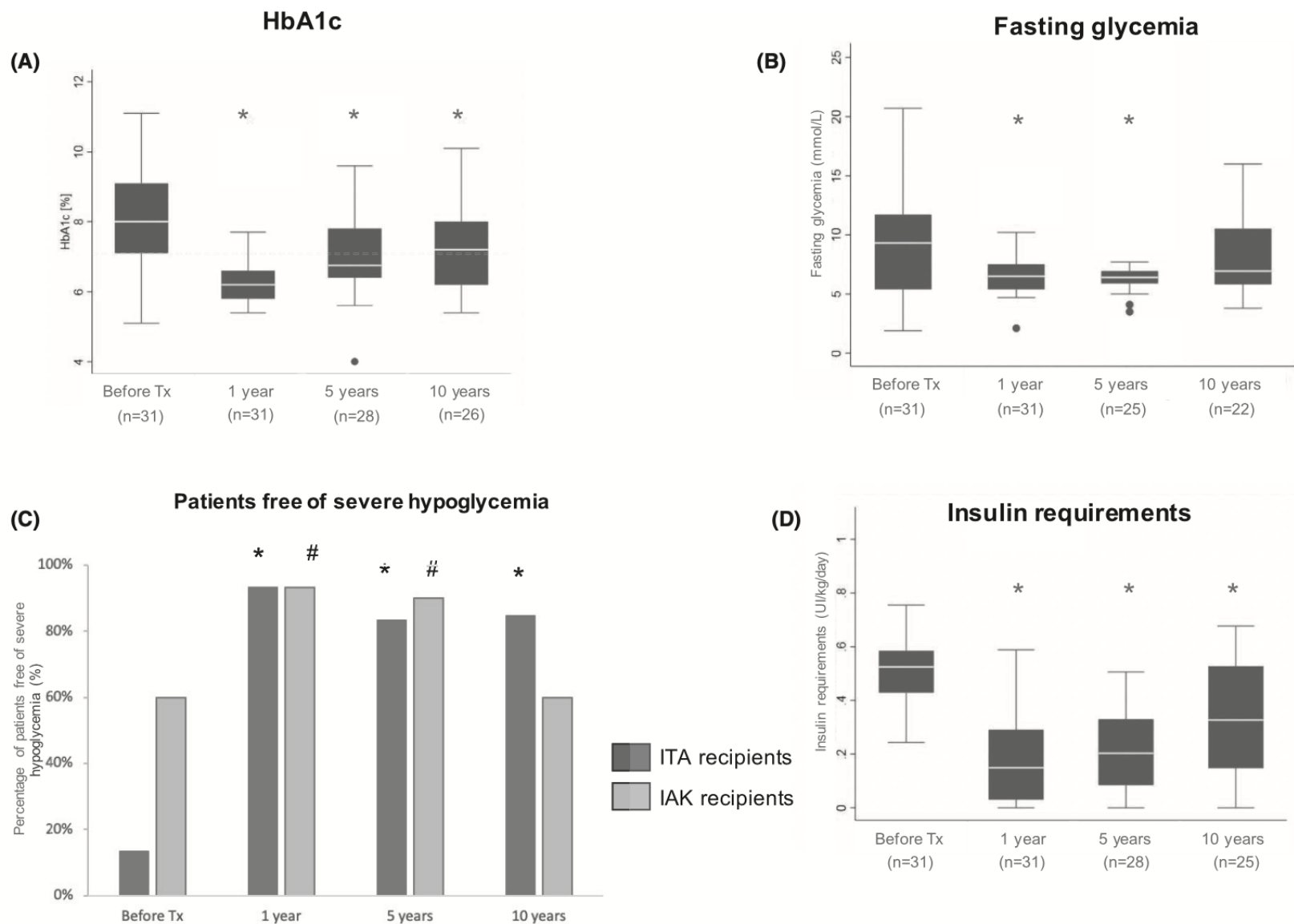
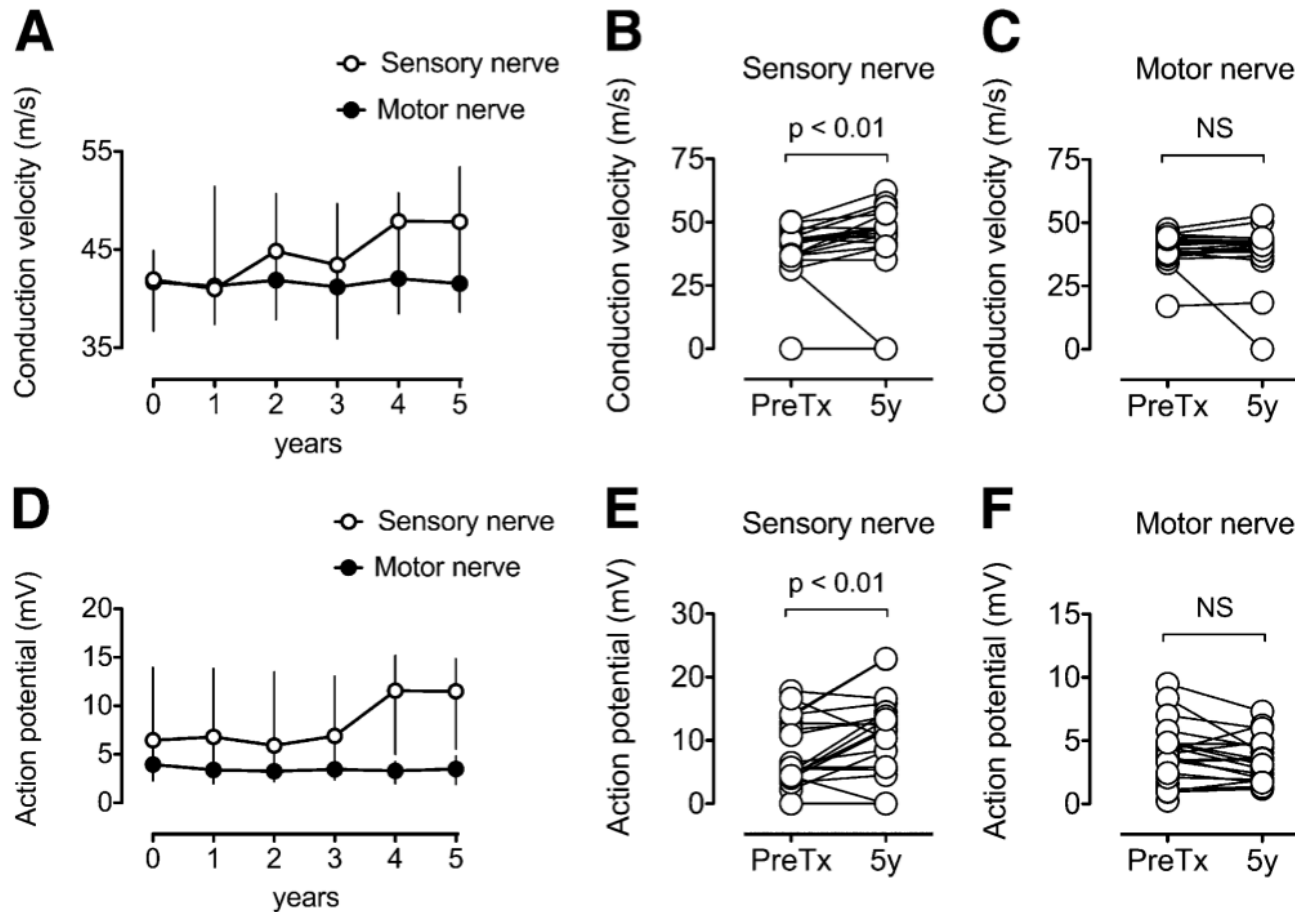


FIGURE 2 (A) Evolution of HbA1c (* $p < .05$ compared to before transplantation status), (B) fasting glycemia (* $p < .05$ compared to before transplantation status), (C) percentage of patients free of severe hypoglycemia (* $p < .05$ as compared to ITA recipients before transplantation, # $p < .05$ as compared to IAK recipients before transplantation), (D) insulin requirements over follow-up

Improvement of Electrophysiological Neuropathy after Islet Transplantation for Type 1 Diabetes: A 5-year Prospective study



Reduced progression of diabetic microvascular complications with Islet cells transplantation compared with intensive medical therapy

TABLE 2. Annual rate of change in GFR by ^{99m}Tc -DTPA and MDRD in the medical and post-ICT groups

Δ GFR (mL/min/1.73 m ² /yr)	Medical (95% CI)	ICT (95% CI)	<i>P</i>
^{99m}Tc -DTPA all subjects	-2.98 (-1.81 to -4.15)	-1.27 (-0.50 to -2.04)	<0.0001
≥2-yr follow-up	-4.79 (-2.44 to -7.14)	-1.42 (-0.44 to -2.40)	<0.0001
≥3-yr follow-up	-3.55 (-1.53 to -5.57)	-1.40 (-0.32 to -2.48)	<0.0001
MDRD all subjects	-3.53 (-2.49 to -4.57)	-1.49 (-1.06 to -1.92)	<0.0001

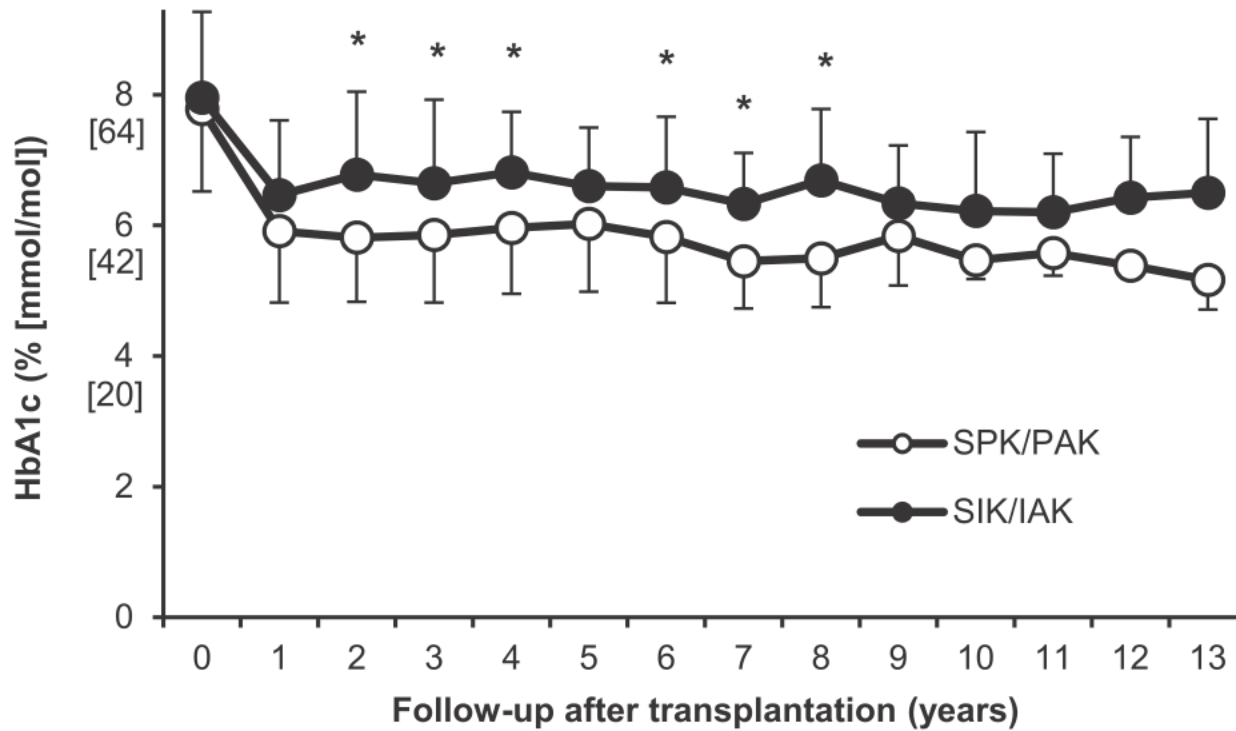
GFR, glomerular filtration rate; ICT, islet cell transplantation; DTPA, ^{99m}Tc -diethylenetriaminepentaacetate; MDRD, modification of diet in renal disease; CI, confidence interval.

TABLE 3. Progression of diabetic retinopathy in the medical and post-ICT groups

	Medical		ICT	
	No. eyes	No. progressed	No. eyes	No. progressed
Mild NPDR	16	0	8	0
Moderate NPDR	19	1	12	0
Severe NPDR	6	2	2	0
PDR	41	7	29	0
Total	82	10 ^a	51	0 ^a

^a The progression is significantly more in the medical than the post-ICT group ($P < 0.01$).

Glycemic control in Islet versus Pancreas Transplantation in Type 1 diabetes with ESRD



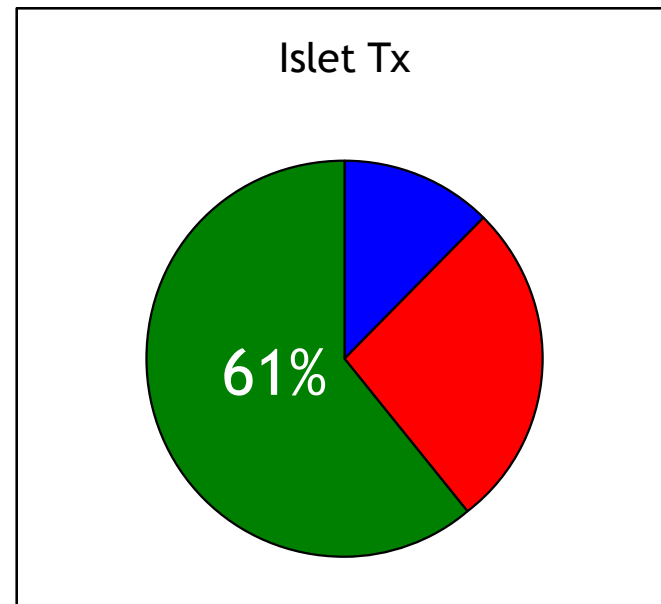
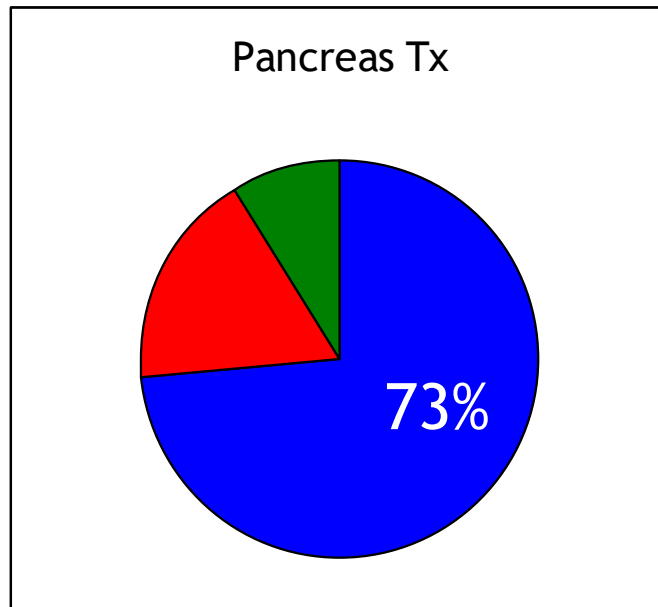
n (SPK/PAK)	86	71	61	45	38	31	23	15	14	13	11	6	6
n (SIK/IAK)	37	30	27	25	18	15	14	9	8	6	4	4	3

Summary: Pancreas versus islet

 Simultaneous with kidney

 After Kidney

 Alone



Procedural risk

Major procedural risk

Minor procedural risk

Immunosuppression

Life-long Immunosuppression

Life-long immunosuppression

ESRD

Consider SPK

Avoid

Functional renal transplant

PAK : glycemic lability
Severe hypoglycemia

IAK : glycemic lability
Severe hypoglycemia

Plan

- Indications
- Survie du patient et du greffon
- Impact sur le diabète et ses complications
- **Immunosuppression**
- Stratégie de greffe chez le patient diabétique de type 1

Immunosuppression

Pancreas

- Induction par ATG ou anti-IL2R
- Traitement de base par Tacrolimus et MMF
- L'arrêt ou l'éviction des stéroïdes n'a pas montré son intérêt par des études randomisées

Ilots

- Induction par ATG ou anti-IL2R
- Traitement de base par Tacrolimus et MMF
- Pas de stéroïdes pour ITA
- Stéroïdes low doses pour IAK

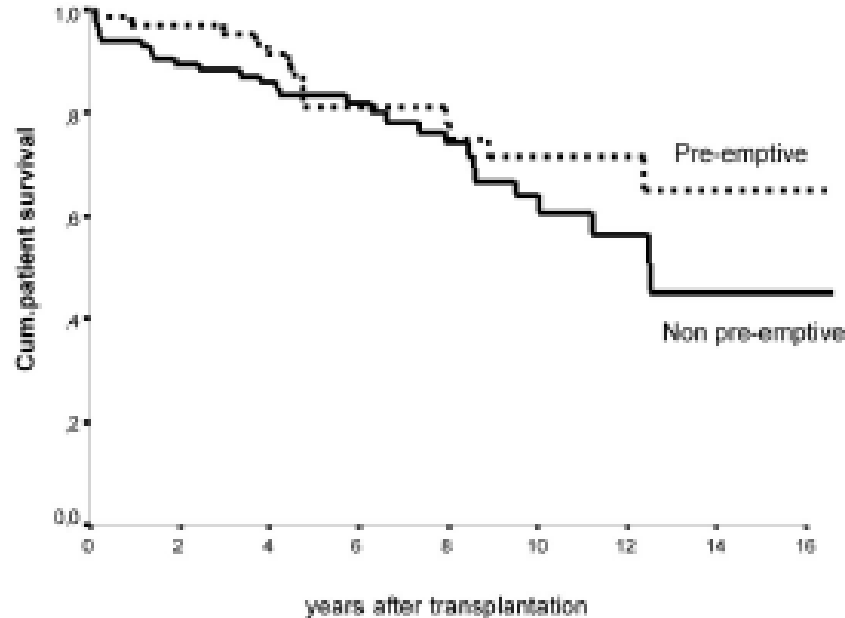
Plan

- Indications
- Survie du patient et du greffon
- Impact sur le diabète et ses complications
 - Transplantation de pancréas
 - Greffe d'îlots
- Immunosuppression
- Stratégie de greffe chez le patient diabétique de type 1

Des indications complexes

- Chez le patient DID I sans insuffisance rénale
 - Pancréas ou îlots ou pancréas artificiel ?
- Chez le patient DID I avec insuffisance rénale chronique (DFG < 50 ml/mn)
 - Rein pancréas combiné ?
 - Rein îlots combiné ?
 - Pancréas après rein ?
 - Ilots après rein ?
 - Savoir si le rein suit le pancréas (diabète instable)
 - Ou si le pancréas suit le rein (DFG < 20 ml/mn)

Greffe rénale préemptive ou non?



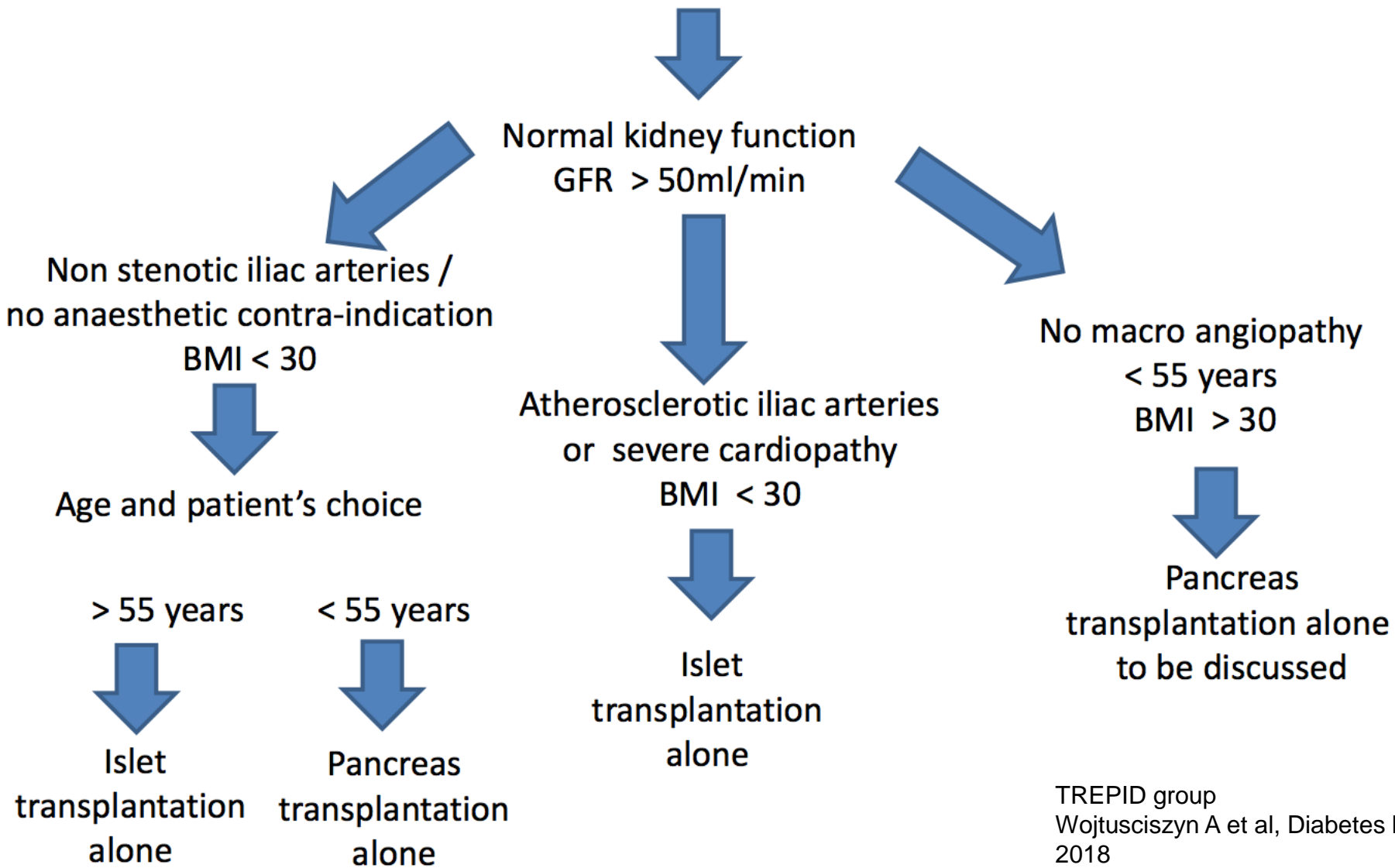
Cause of death	Pre-emptive	Non pre-emptive	P-value
Cardiac	2 (3.1%)	11 (9.6%)	0.044
Infection	5 (7.7%)	6 (5.2%)	NS
Other ^a	7 (10.8%)	14 (12.2%)	NS

^a Ranging from malignancies, major bleedings, thromboembolic complications, suicide, to unknown.

Key parameters to define transplant strategy in type 1 diabetic patients

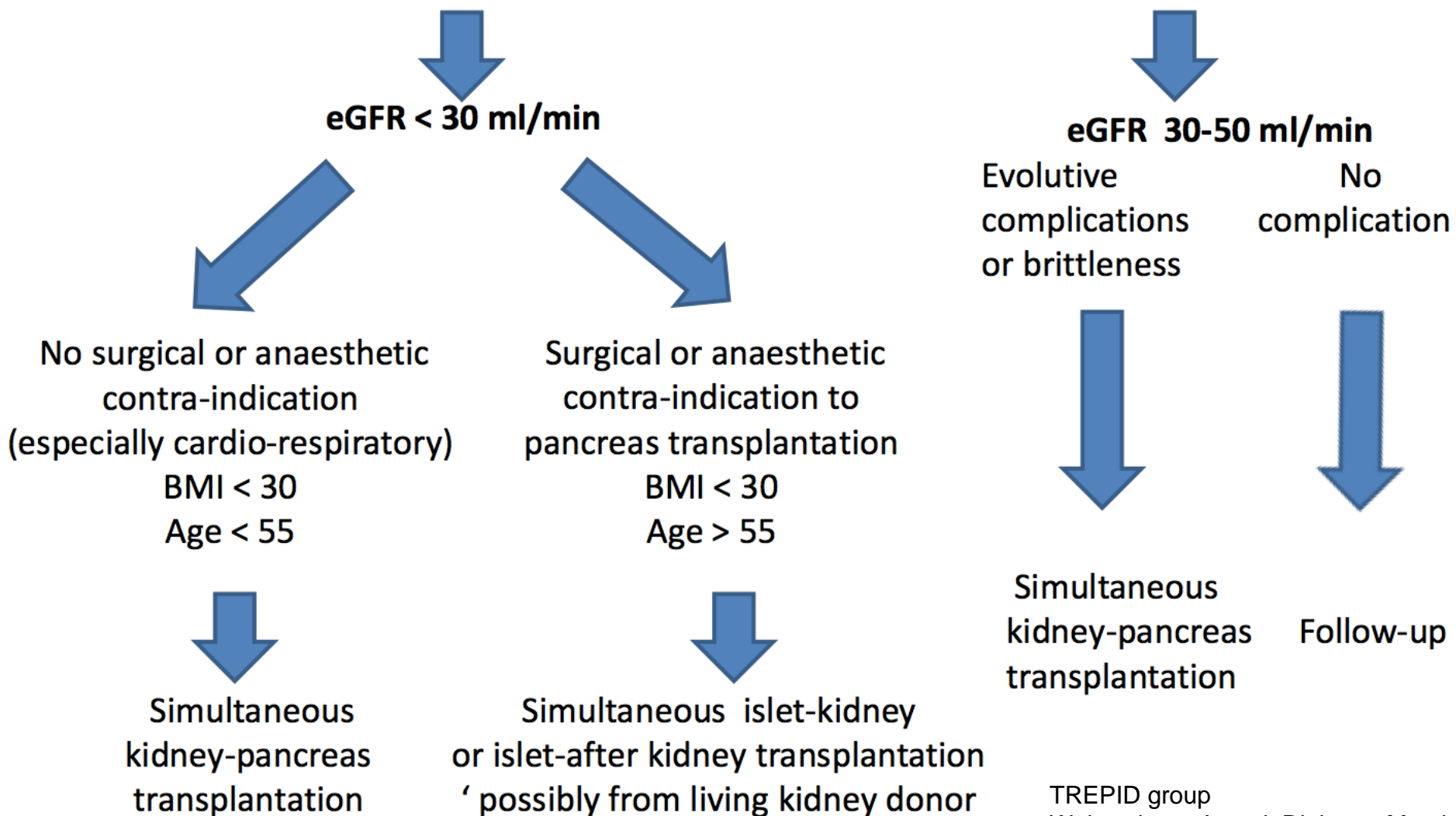
- Age (priority < 55 years)
- Sensitization
- Number of transplantation (priority first transplantation)
- Renal function
 - GFR > 50 ml/mn: Islet or pancreas
 - GFR <30 ml/m: kidney graft mandatory
- Diabetic control:
 - Hb A1c, severe hypoglycemia, microvascular complications
- Surgical risk:
 - coronary disease, iliac arterial calcifications, BMI <27 kg/m²

TYPE 1 DIABETES
POOR GLYCEMIC BALANCE AND/OR SEVERE HYPOGLYCEMIA
Multi-injections or insulin pump ± CGM



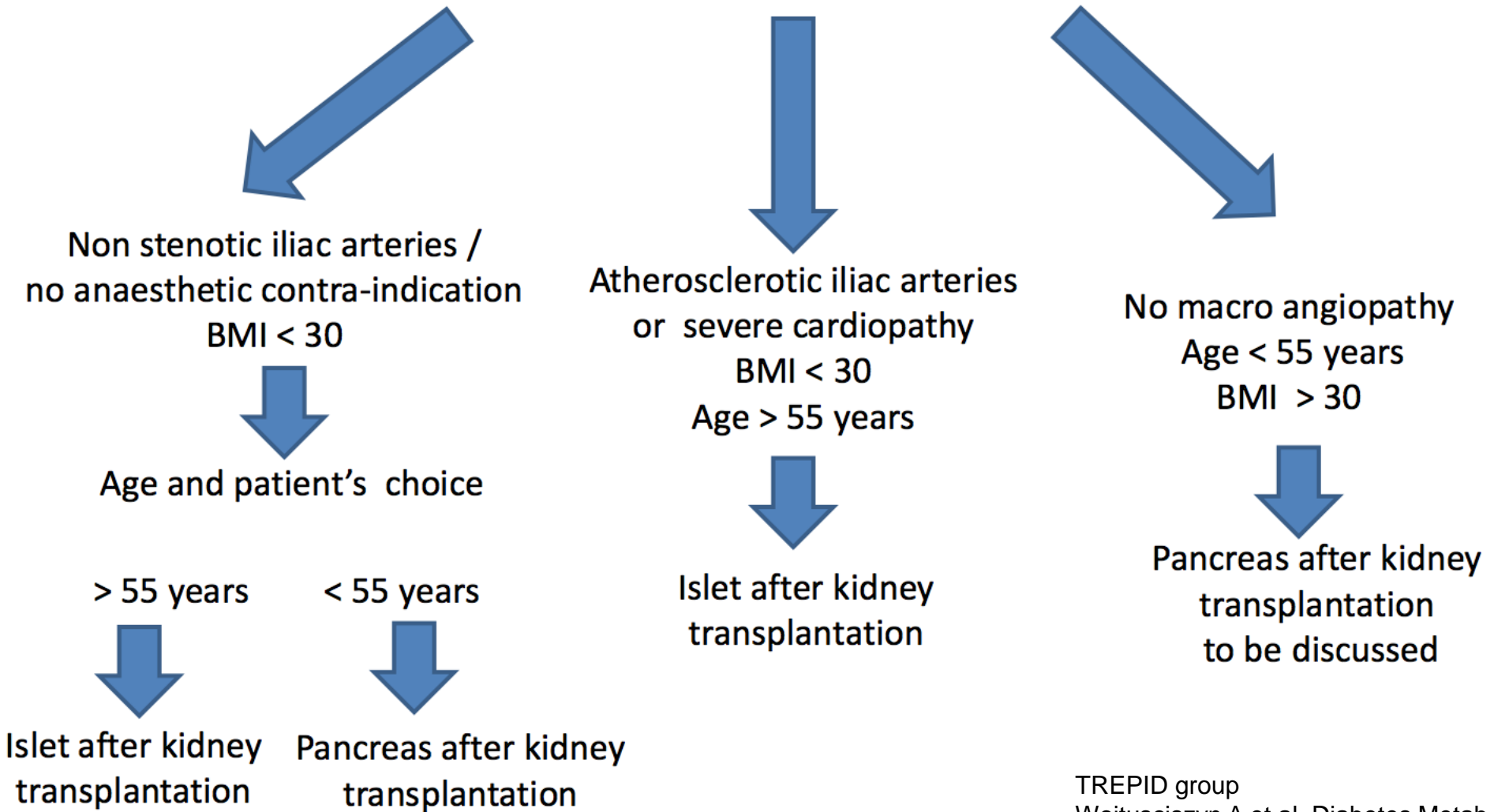
TYPE 1 DIABETES + REDUCED eGFR

Multi-injections or insulin pump ± CGM



TYPE 1 DIABETES + functional KIDNEY GRAFT

HbA1c \geq 7% or severe hypoglycemia

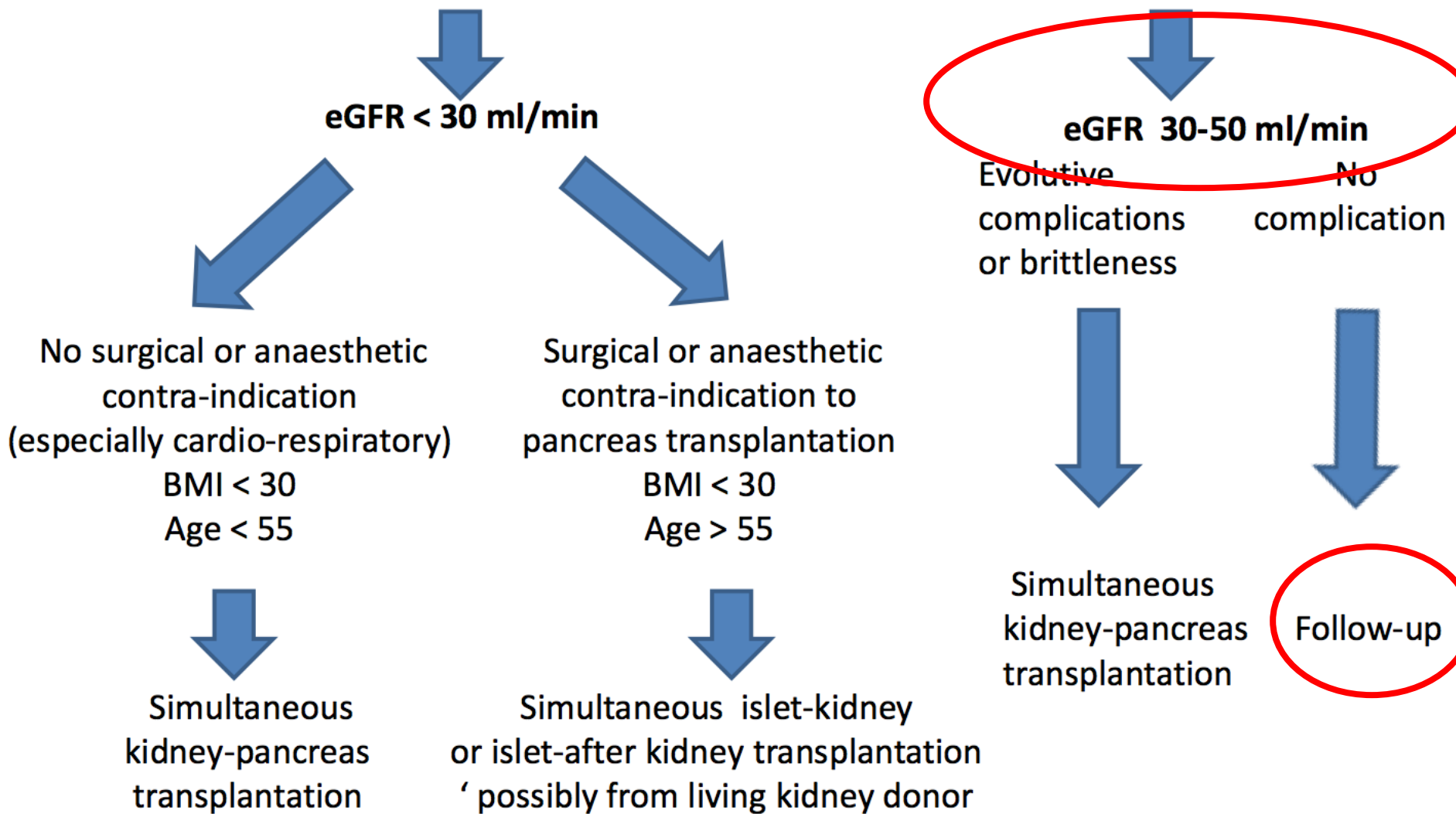


Case report 1

- Female 42 years old
- Type 1 diabetes
- Diabetes duration: 24 years
- Hb A1C 8.5% Insulin therapy: Implantable pump
- Hypoglycemia: once a day, no severe hypoglycemia
- Diabetes complication: neuropathy, retinopathy, nephropathy
- GFR : 44 ml/mn/1.73m² (CKD EPI)
- Blood Group: AB
- No evidence for macroangiopathy

TYPE 1 DIABETES + REDUCED eGFR

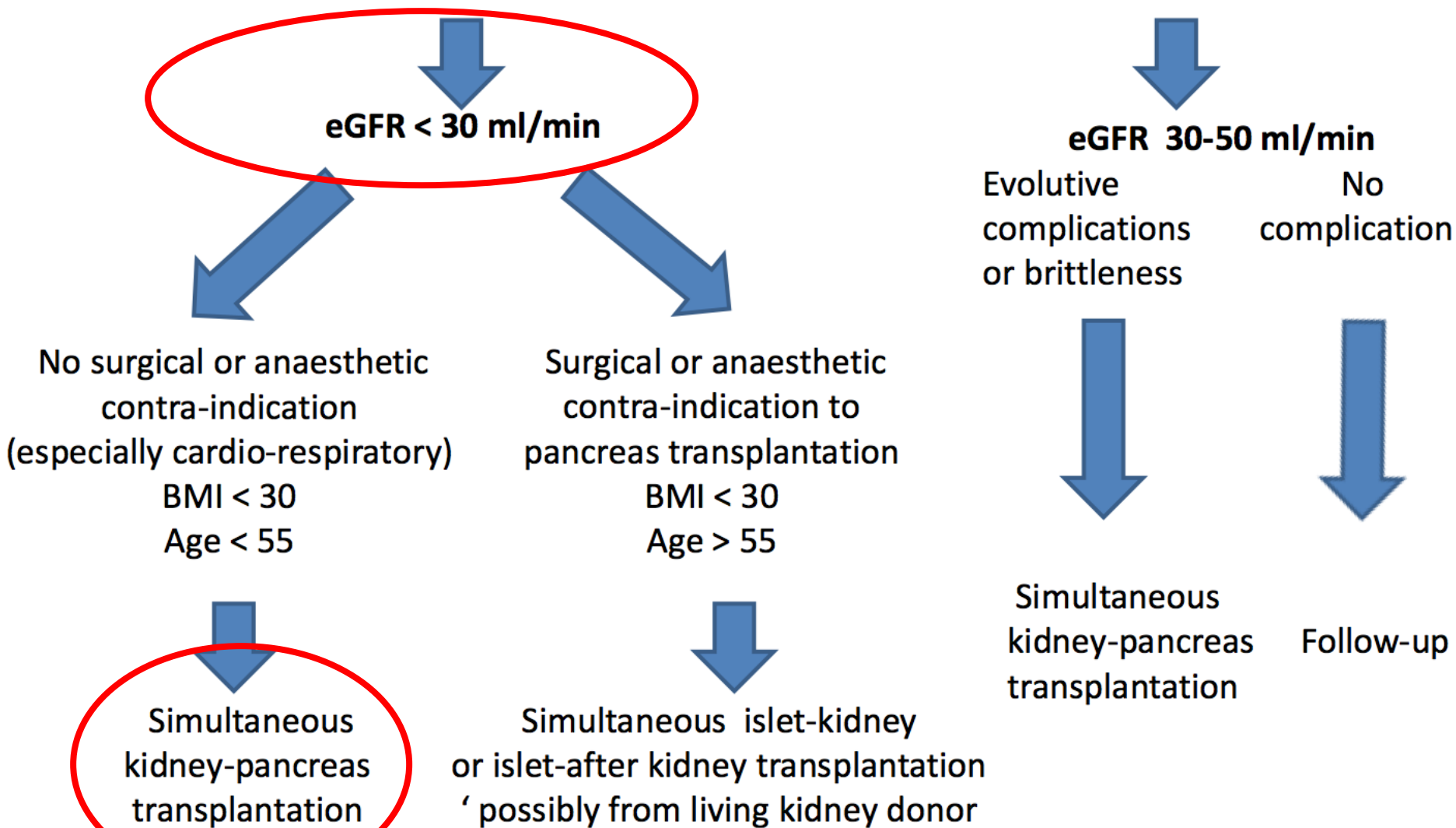
Multi-injections or insulin pump ± CGM

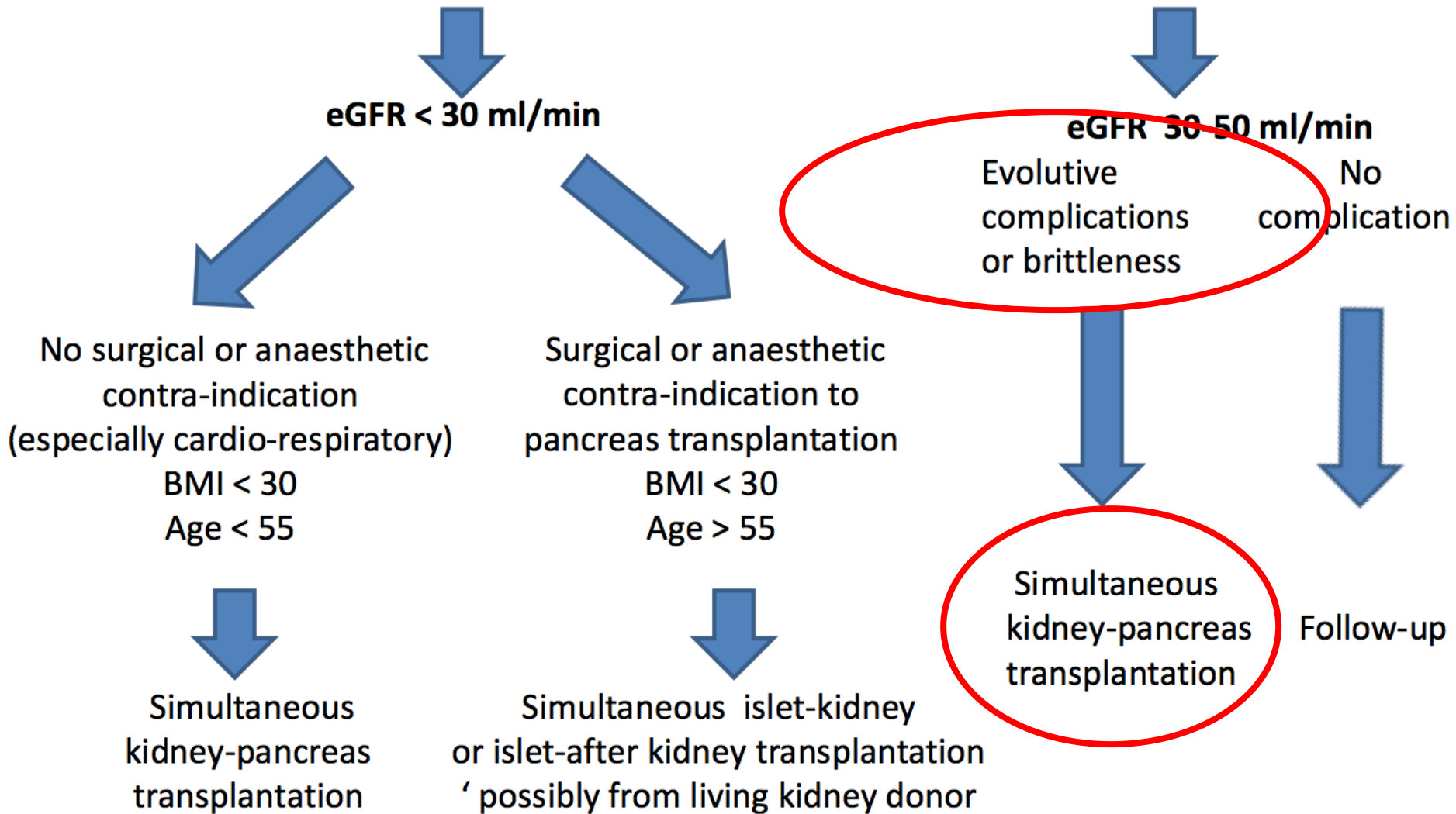


2A

TYPE 1 DIABETES + REDUCED eGFR

Multi-injections or insulin pump ± CGM



TYPE 1 DIABETES + REDUCED eGFR**Multi-injections or insulin pump ± CGM**

Case report 2

- Female 27 years old
- Type 1 diabetes
- BMI 22 kg/M2
- Diabetes duration: 18 years
- Hb A1C 10.5% Insulin therapy: Lantus 24 UI/day
- Hypoglycemia: 3/weeks, no severe hypoglycemia
- Diabetes complication: neuropathy, retinopathy, nephropathy
- Hemodialysis for 4 years
- Blood Group: AB
- No evidence for macroangiopathy
- Anti HLA antibodies: PRA class I: 70%

2A

TYPE 1 DIABETES + REDUCED eGFR

Multi-injections or insulin pump ± CGM

eGFR < 30 ml/min

eGFR 30-50 ml/min

Evolutionary complications
or brittleness

No complication

No surgical or anaesthetic
contra-indication
(especially cardio-respiratory)

BMI < 30

Age < 55

Surgical or anaesthetic
contra-indication to
pancreas transplantation

BMI < 30

Age > 55

Simultaneous
kidney-pancreas
transplantation

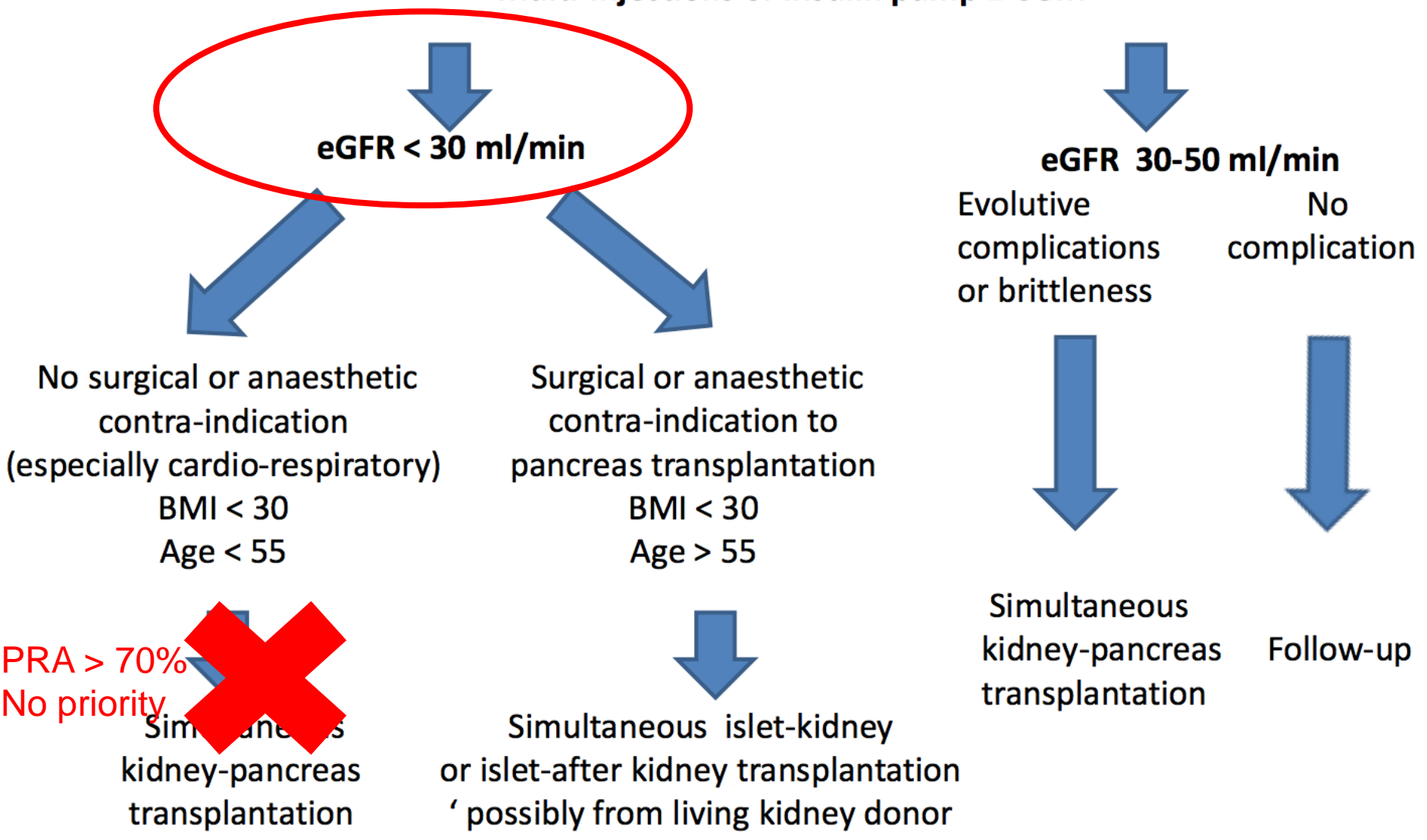
Simultaneous islet-kidney
or islet-after kidney transplantation
'possibly from living kidney donor

Simultaneous
kidney-pancreas
transplantation

Follow-up

TYPE 1 DIABETES + REDUCED eGFR

Multi-injections or insulin pump ± CGM



2A

TYPE 1 DIABETES + REDUCED eGFR

Multi-injections or insulin pump ± CGM

eGFR < 30 ml/min

eGFR 30-50 ml/min

Evolutionary complications
or brittleness

No complication

No surgical or anaesthetic
contra-indication
(especially cardio-respiratory)

BMI < 30
Age < 55

Surgical or anaesthetic
contra-indication to
pancreas transplantation

BMI < 30
Age > 55

Kidney Transplantation
Living donor > Dcd donor

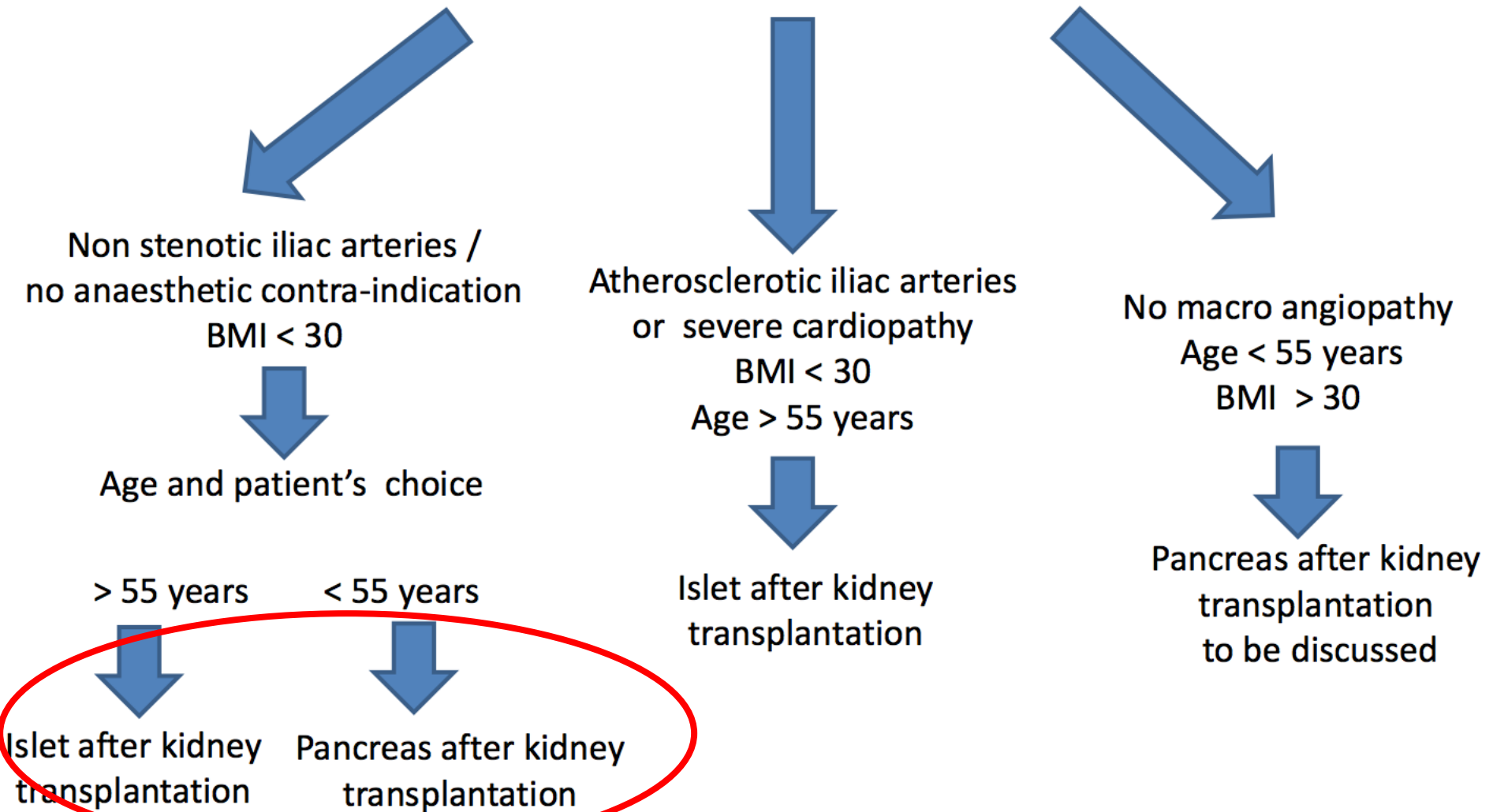
Simultaneous islet-kidney
or islet-after kidney transplantation
/ possibly from living kidney donor

Simultaneous
kidney-pancreas
transplantation

Follow-up

TYPE 1 DIABETES + functional KIDNEY GRAFT

HbA1c \geq 7% or severe hypoglycemia



Greffe d'îlots de Langerhans: de la recherche à la routine !!!

9 mars 2021

JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE

Texte 15 sur 131

Décrets, arrêtés, circulaires

TEXTES GÉNÉRAUX

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

Arrêté du 5 mars 2021 modifiant l'arrêté du 19 février 2015 relatif aux forfaits alloués aux établissements de santé mentionnés à l'article L. 162-22-6 du code de la sécurité sociale ayant des activités de médecine, obstétrique et odontologie ou ayant une activité d'hospitalisation à domicile

Art. 2. – L'article 6 est complété par un 27° ainsi rédigé :

« 27° Lorsque les prestations de séjour et de soins délivrées au patient donnent lieu à la production d'un des GHM de la racine 27C03 "Transplantations pancréatiques", la prise en charge du patient donne lieu à facturation d'un des GHS suivants :

« – dès lors qu'un acte de transplantation d'îlots pancréatiques, par injection dans la veine porte par voie transcutanée avec guidage radiologique (HNEH900), a été réalisé, la production du GHM 27C031, 27C032, 27C033 ou 27C034 donne lieu à facturation du GHS 8940 ;

Acknowledgments

- Transplantation, nephrology and clinical immunology :
 - M Brunet F Buron C Levi S Daoud O Thauinat R Cahen, C Pouteil-Noble, Antoine Sicard, A Koenig, C Fournie
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- Anesthesiology/Intensive care unit :
 - T Rimmelle- A Bertin- C Jadaud- G Marcotte
- Surgical team
 - L Badet
 - X Martin
 - R Cudas
 - H Fassi Fehri
 - M Colombel
 - S Crouzet
- Gragil network :
 - T Berney, PY Benhamou, L Kessler....
- TREPID group
 - Esposito AL, Badet L, Gragil, Paris, Lille's groups

Merci

