Gestion et adaptation du traitement immunosuppresseur chez le patient diabétique

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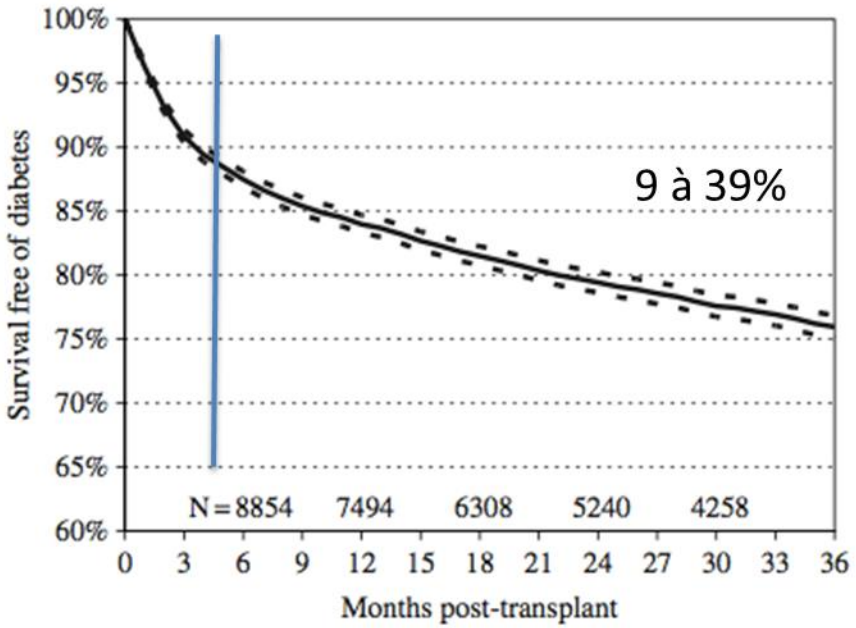
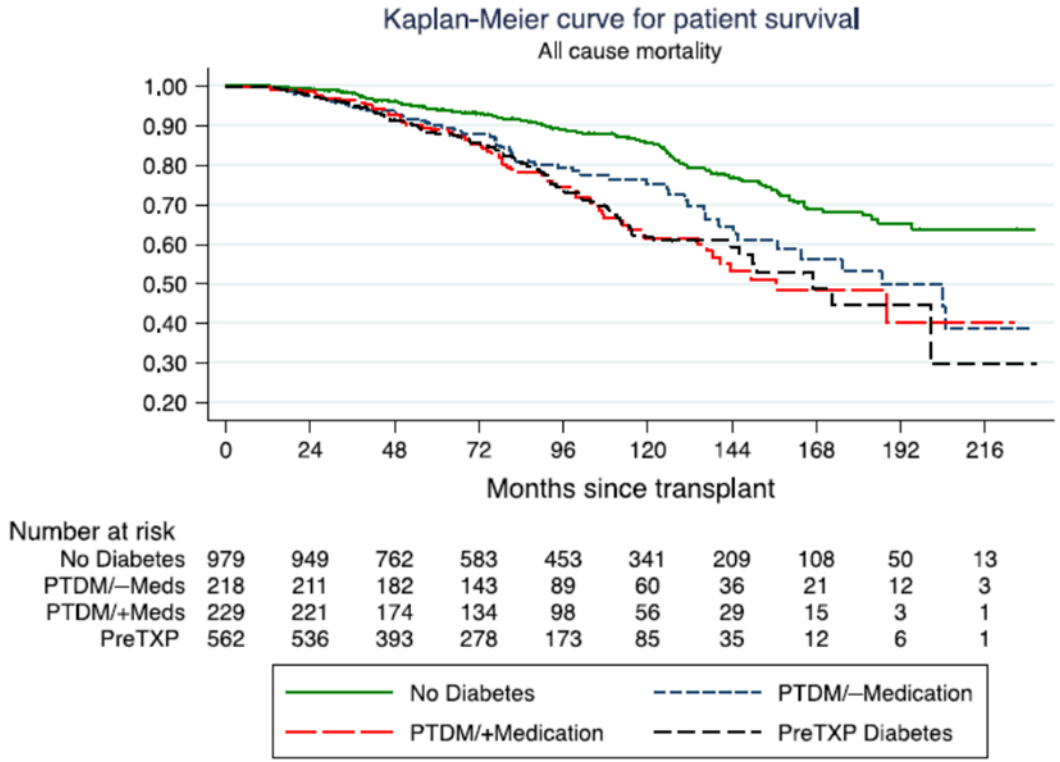
Quel contexte ?

Augmentation de l'accès sur liste des patients DT2

Forte incidence du PTD

Pronostic péjoratif





Dienemann Transplant Int 2016

Quelles questions ?

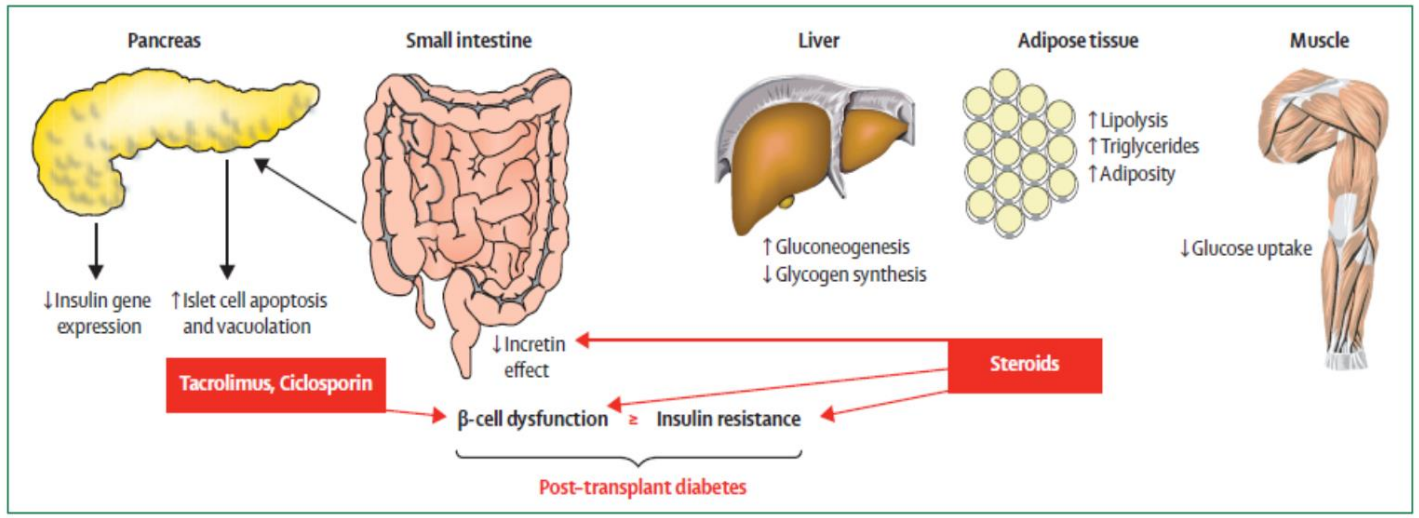
Patient diabétique après transplantation
DPT ou DT2

Améliorer le contrôle du diabète

Faut-il modifier l'immunosuppression ?

	Mechanism of action	Advantages	Disadvantages
Biguanides (metformin)	Suppression of hepatic gluconeogenesis and insulin sensitising	Efficacy (microvascular and macrovascular endpoints), no hypoglycaemia, no weight gain, drug cost	Gastrointestinal side-effects, limitations for use in renal impairment
Sulphonylureas (glipizide, gliclazide, etc)	Stimulation of insulin secretion	Efficacy (microvascular endpoints), drug cost	Hypoglycaemia, weight gain, accumulates in renal failure
Thiazolidinediones (rosiglitazone, pioglitazone)	Insulin sensitising	Sustained glucose control	Weight gain, oedema, drug cost, adverse cardiovascular effects
Meglitinides (repaglinide, nateglinide)	Stimulation of insulin secretion	Reduces postprandial hyperglycaemia, safe with advancing renal failure (repaglinide)	Hypoglycaemia, weight gain, drug cost, dose adjustment in renal failure (nateglinide)
Alpha glucosidase inhibitors (acarbose)	Decreases gastrointestinal carbohydrate absorption	No hypoglycaemia, weight neutral	Gastrointestinal side-effects
GLP-1 agonists (exenatide, liraglutide)	Stimulates insulin secretion, decreases glucagon production, stimulates satiety	No weight gain (possible reduction), low risk of hypoglycaemia, lowers blood pressure, safety in renal impairment (liraglutide)	Gastrointestinal side-effects, risk of pancreatitis altered drug absorption, drug cost, renal impairment, antibody production (exenatide)
DPP-4 inhibitors (sitagliptin, vildagliptin, linagliptin)	Decreases inactivation of incretins (GLP-1)	No weight gain, safety in renal impairment	Drug cost, risk of pancreatitis, putative link to certain cancers
Insulin	Exogenous administration of primary glycaemia countering hormone	Efficacy (microvascular and macrovascular endpoints), no ceiling of treatment, range of insulin types for individualisation	Weight gain, subcutaneous administration, hypoglycaemia, putative link to certain cancers
Sodium-dependent glucose transporters (SGLT)2 inhibitors	Block renal glucose reabsorption in the proximal tubule	Possible natriuretic effect, action independent of insulin, little risk of hypoglycaemia	Glycosuria might increase risk of genitourinary infections and exacerbate profibrotic pathways, risk of dehydration, ketoacidosis risk
Glucokinase inhibitors	Activate glucokinase glucose sensors in pancreatic and hepatic cells	Dual action on both liver and pancreas, weight neutral (possible reduction)	Safety (glucokinase expressed in neuronal cells), effect on kidney unknown
Glucagon antagonists	Blocks the antagonistic action of glucagon versus insulin	Glucagon integral to whole body glucose homoeostasis	Awaiting further investigation
Bile acid sequestrants (cholestyramine, colestimide, colesevelam)	Unknown (possible pleiotropic effect of lipid lowering)	Beneficial effects on abnormal lipid profiles, safe in renal impairment	Gastrointestinal side-effects very common, disruption of fat-soluble vitamin absorption
Amylin analogues	Synthetic analogue of β-cell hormone amylin—delays gastric emptying, increases satiety, and inhibits glucagon production	Weight neutral (possible reduction), safe in mild-to-moderate renal impairment	Subcutaneous administration, risk of hypoglycaemia, gastrointestinal side-effects, not available outside USA

Impact des immunosuppresseurs



	Post-transplant diabetes
Corticosteroids*	Increased
Tacrolimus*	Increased
Ciclosporin*	Slightly increased
mTORi*	Slightly increased
Mycophenolic acid*	..
Azathioprine*	..
Belatacept*	Slightly decreased?
Basiliximab†	Slightly increased?
Monoclonals†	..

Sharif Lancet 2016

Quelle physiopathologie ?

	DT1	DT2	DPT
Physiopathologie	Déficit en Io (immun)	Résistance à l'Io (+/- réduction de la sécrétion d'Io)	Dysfonction béta en présence d'une résistance à l'Io
Défaut primitif	Insuffisance béta	Résistance à l'Io	Dysfonction béta
Besoins en Io	Essentiel	Parfois	Dépend du moment
Age de début	< 40	> 40	Tout âge (↑ risque)
Effet du mode de vie	Non	Oui	En partie
Risque d'acidocétose	Elevé	Très rare	Rare
Auto-Ac	Présent	Absent	Absent

Mécanismes non univoques

Réflexion et stratégies différentes pour DT2 et PTD ?

D’autres facteurs de risque ?

Aggravation du diabète après transplantation

Survenue de diabète post-transplantation

Intégration dans un contexte global d’interactions

Sédentarité

Prise de poids

Changement de régime

…

Panel 1: Risk factors for development of post-transplant diabetes

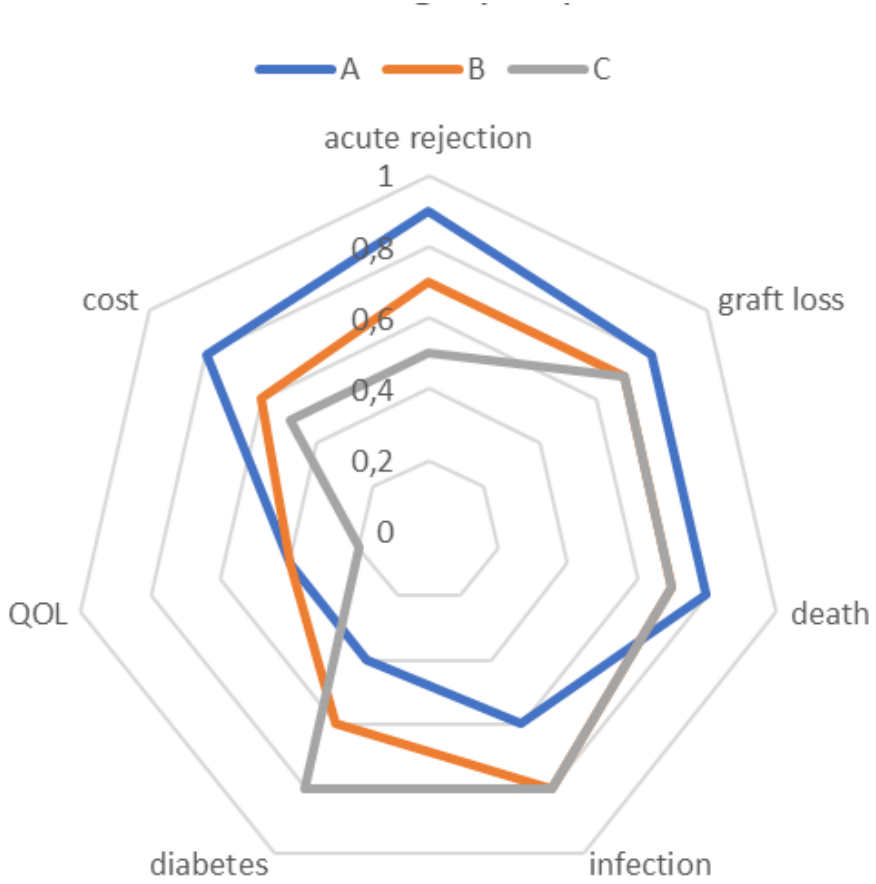
Non-modifiable risk factors

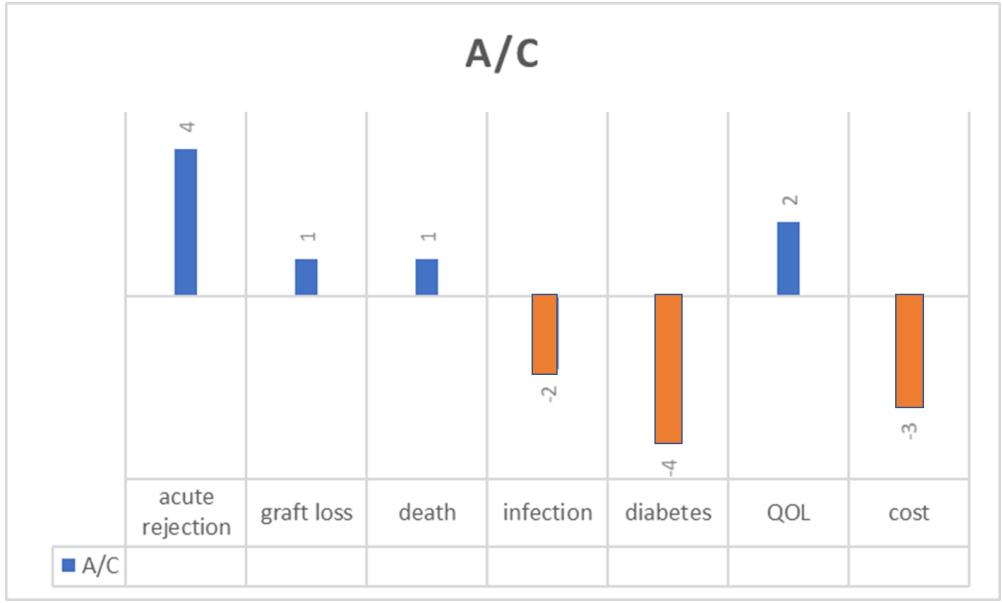
- Age
- Ethnicity
- Family history of diabetes
- Cause of end-stage renal failure*
- Male sex
- Human leucocyte antigen mismatch?*
- Genetic polymorphisms
- Innate immunity*
- Donor characteristics?*

Modifiable risk factors

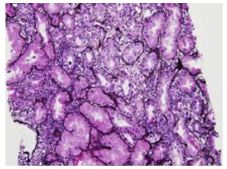
- Immunosuppression*
- Rejection episodes*
- Previous stress diabetes
- Obesity or weight gain
- Metabolic syndrome
- High pretransplantation triglyceride concentration
- Cytomegalovirus infection*
- Hepatitis C virus infection*
- Antihypertensive drugs (eg, β blockers or thiazide diuretics)
- Biochemical abnormalities (eg, low magnesium or high uric acid)

Les modifications agissent sur plusieurs dimensions





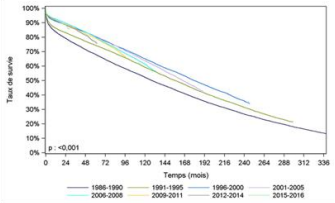
Apprécier l'effet sur les différentes dimensions



Acute rejection

Infection

Contrôle du diabète

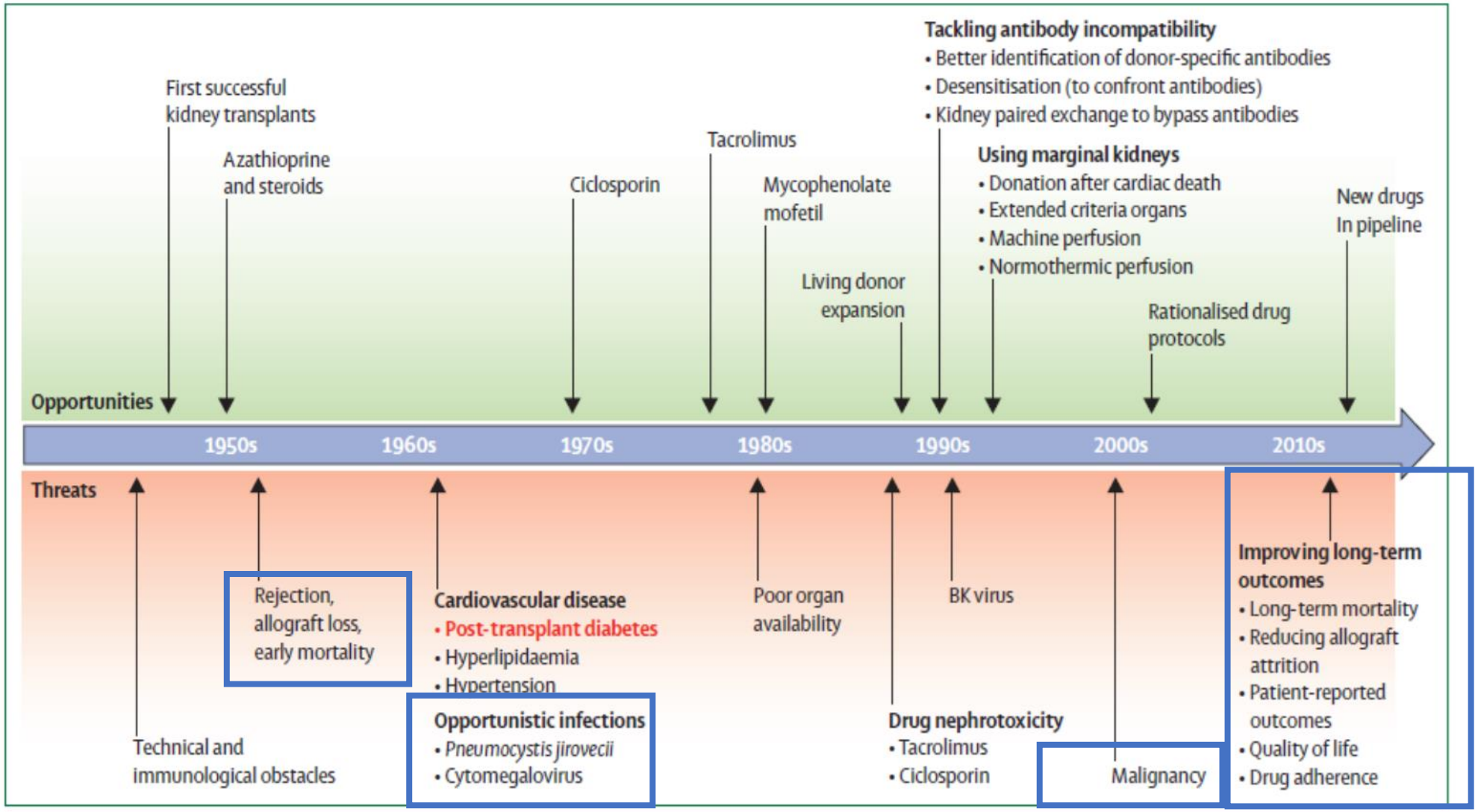


Survie

Notion de balance entre les différents risques

Diminution de l'IS
Tenir compte du risque de rejet aigu

Augmentation de l'IS
Tenir compte du risque infectieux


Tackling antibody incompatibility
• Better identification of donor-specific antibodies
• Desensitisation (to confront antibodies)
• Kidney paired exchange to bypass antibodies
First successful kidney transplants
Azathioprine and steroids
Ciclosporin
Tacrolimus
Mycophenolate mofetil
Living donor expansion
Using marginal kidneys
• Donation after cardiac death
• Extended criteria organs
• Machine perfusion
• Normothermic perfusion
Rationalised drug protocols
New drugs In pipeline
Opportunities
1950s
1960s
1970s
1980s
1990s
2000s
2010s
Threats
Technical and immunological obstacles
Rejection, allograft loss, early mortality
Cardiovascular disease
• Post-transplant diabetes
• Hyperlipidaemia
• Hypertension
Opportunistic infections
• Pneumocystis jirovecii
• Cytomegalovirus
Poor organ availability
Drug nephrotoxicity
• Tacrolimus
• Ciclosporin
BK virus
Malignancy
Improving long-term outcomes
• Long-term mortality
• Reducing allograft attrition
• Patient-reported outcomes
• Quality of life
• Drug adherence

Rationnel de la prévention

2 stratégies :

Celle du transplanteur : modifier l'IS

Celle du diabétologue : modifier le patient

Peu de data post-transplantation
Intégration des données de prévention primaire
(prévention PTD ~ meilleur contrôle DT2)

Modifier l’immunosuppression chez un patient transplanté diabétique

Dans la vraie vie

Medications	Non-diabetes (N=2447)	DM1 (N=166)	DM2 (N=1497)	*p*-value
Transplant specific				
Cyclosporine A	1291 (52.8%)	76 (45.8%)	727 (48.6%)	0.015
Tacrolimus	841 (34.4%)	74 (44.6%)	640 (42.8%)	<0.001
Sirolimus	201 (8.2%)	15 (9.0%)	129 (8.6%)	0.87
Mycophenolate mofetil	1566 (64.0%)	96 (57.8%)	1018 (68.0%)	0.005
Azathioprine	489 (20.0%)	35 (21.1%)	216 (14.4%)	<0.001
Prednisone	2245 (91.7%)	152 (91.6%)	1341 (89.6%)	0.07
Calcineurin inhibitors (CI)	2130 (87.1%)	150 (90.4%)	1360 (90.9%)	0.001
Bone marrow suppressants (BMS)	2042 (83.5%)	131 (78.9%)	1229 (82.2%)	0.21

Weinrauch Int J Nephrol Renovasc Dis 2017

Minimisation ou épargne des CNI

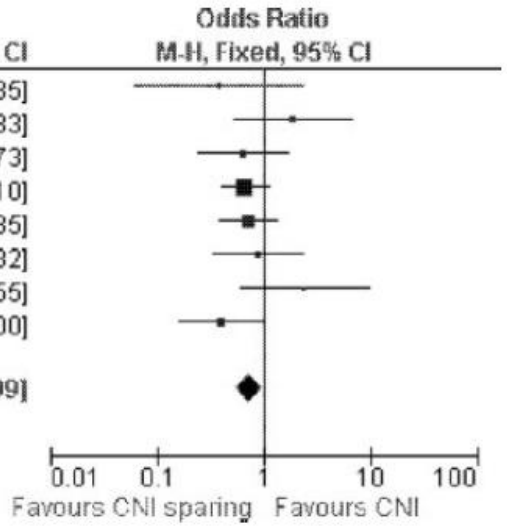
Effet dose : Minimisation

Effet molécule : Epargne

56 études
11337 patients
Réduction de 26% (1-45) du risque

Study or Subgroup	CNI sparing Events	Total	CNI Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Asberg 2006	2	23	4	20	3.6%	0.38 [0.06, 2.35]
Chan 2008	8	49	4	43	3.3%	1.90 [0.53, 6.83]
Durrbach 2010	7	175	11	184	9.4%	0.66 [0.25, 1.73]
Ekberg-2 2007	30	399	43	401	36.4%	0.68 [0.42, 1.10]
Ekberg-3 2007	19	399	25	390	22.1%	0.73 [0.40, 1.35]
Hernandez 2007	9	80	10	80	8.1%	0.89 [0.34, 2.32]
Salvadori 2009	7	142	3	143	2.6%	2.42 [0.61, 9.55]
Vincenti 2010	7	211	16	204	14.4%	0.40 [0.16, 1.00]
Total (95% CI)		**1478**		**1465**	**100.0%**	**0.74 [0.55, 0.99]**
Total events	89		116			

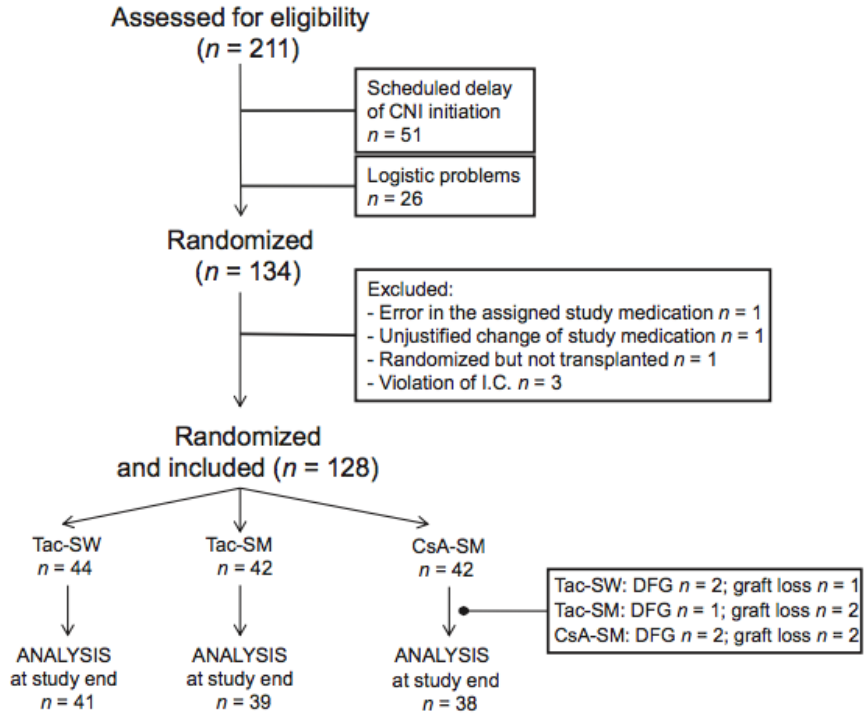
Heterogeneity: Chi² = 7.51, df = 7 (P = 0.38); I² = 7%
Test for overall effect: Z = 2.06 (P = 0.04)

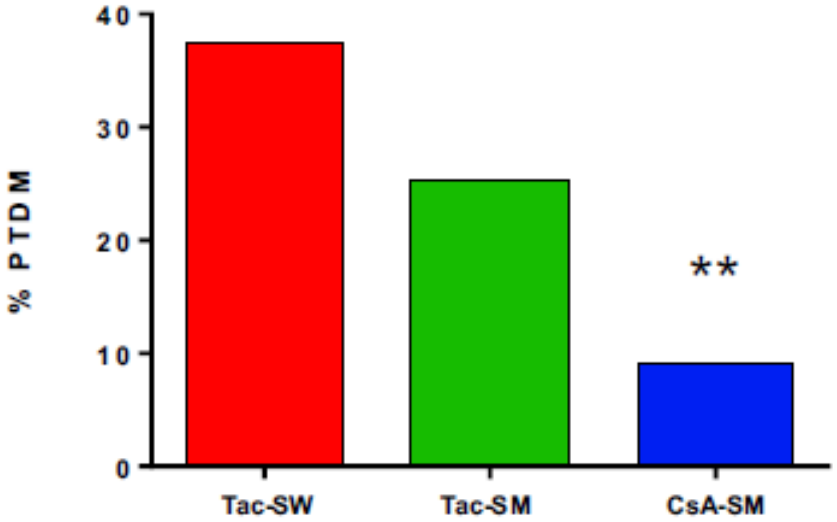


Interprétation difficile des effets connexes
Multiplicité des approches thérapeutiques

Sharif J Am Soc Nephrol 2011

Tacrolimus vs CsA





	TAC-SW	TAC-SM	CsA-SM	p
PTDM 1 an	37,8%	25,7%	9,7%	**0,03**
Echec *	38,6%	42,9%	71,4%	**0,005**

Torres Kidney Int Rep 2018

Tacrolimus vs CsA

Après transplantation

Conversion tardive du tacrolimus vers la ciclosporine

	CYC (n = 43)	TAC (n = 41)	P
Months to diagnosis of PTDM	2.4 (0.3-13.0)	2.6 (0.5-19.2)	.42
Months from PTDM diagnosis to inclusion	23.5 (9.7-51.3)	16.3 (7.0-30.8)	.12
Months from transplantation to inclusion	34.0 (18.6-90.5)	27.8 (10.5-69.3)	.19

Patients avec PTD avéré

Insulin therapy, n	16/43 (37%)	15/41 (37%)	.95
Insulin dosage, units/d (IQR)	22 (12-30)	16 (12-24)	.56
Oral agent(s),[c] n	19/43 (44%)	19/41 (46%)	.84
No glucose-lowering treatment, n	10/43 (23%)	9/41 (22%)	.89
HbA_{1c}, %	6.49 ± 0.85	6.84 ± 0.80	.08

Ayant un diabète bien contrôlé

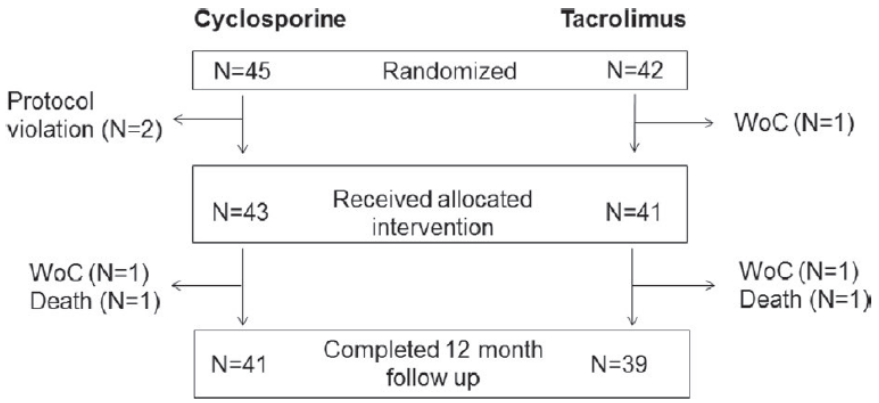
PRA at transplantation (>5%),[b] n	3/41 (7.3%)	3/39 (7.7%)	.95
PRA historic maximum (>5%),[b] n	5/41 (12.2%)	6/39 (15.4%)	.68
History of acute rejection, n	11/41 (27%)	7/41 (17%)	.42
Steroid free, n	21/43 (49%)	20/41 (49%)	.99
Tacrolimus trough concentration, ng/mL	7.3 ± 2.2	8.3 ± 3.5	.13

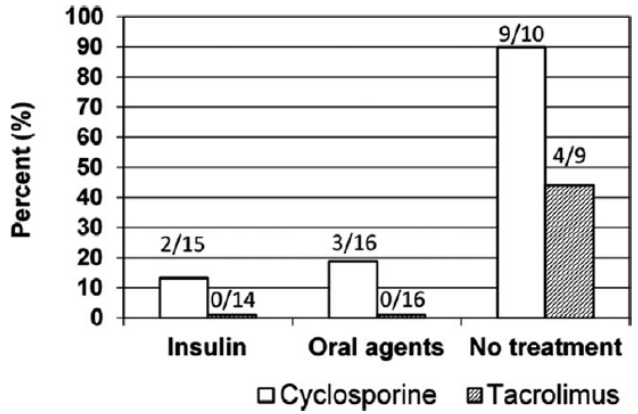
Risque immunologique « moyen »
Résiduels tacrolimus élevés

Wissing Am J Transplant 2017

Tacrolimus vs CsA

Après transplantation





(B)		HbA_{1c} <6.0%	P	HbA_{1c} <6.5%	P
Overall cohort					
	CYC	21/41 (51%)	<.0001	28/41 (68%)	.003
	TAC[c]	3/38 (8%)		13/38 (34%)	

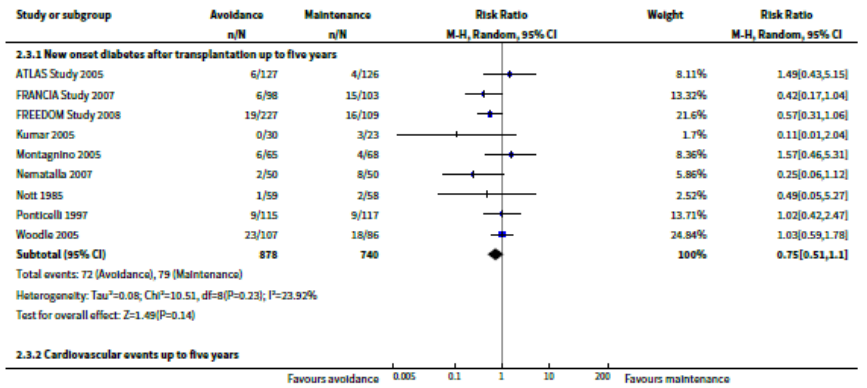
	Baseline	3 months	6 months	9 months	12 months	P[a]
Patients without glucose-lowering therapy, n						
CYC[b]	10/43 (23%)	10/39 (26%)	10/40 (25%)	12/39 (31%)	16/41 (39%)	.01
TAC[c]	9/41 (22%)	6/39 (15%)	5/39 (13%)	5/38 (13%)	5/38 (13%)	

Wissing Am J Transplant 2017

Stéroïdes

19 études
3401 participants

Analysis 2.3. Comparison 2 Steroid avoidance versus steroid maintenance, Outcome 3 New-onset diabetes after transplantation and cardiovascular events.

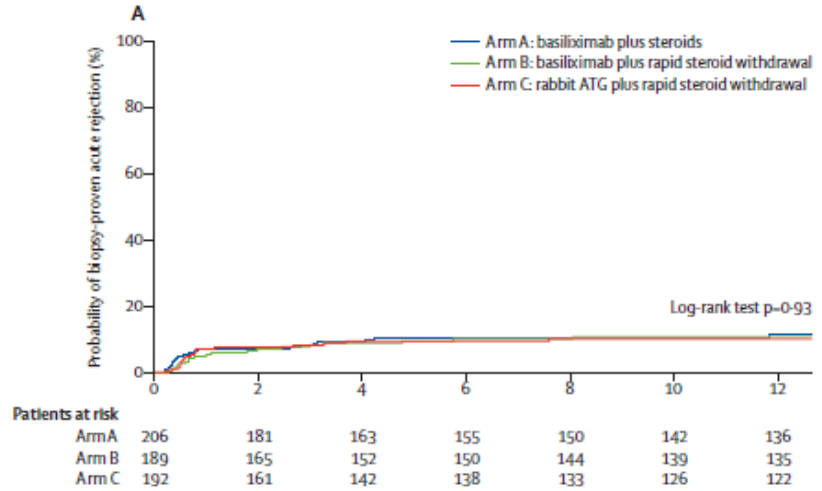


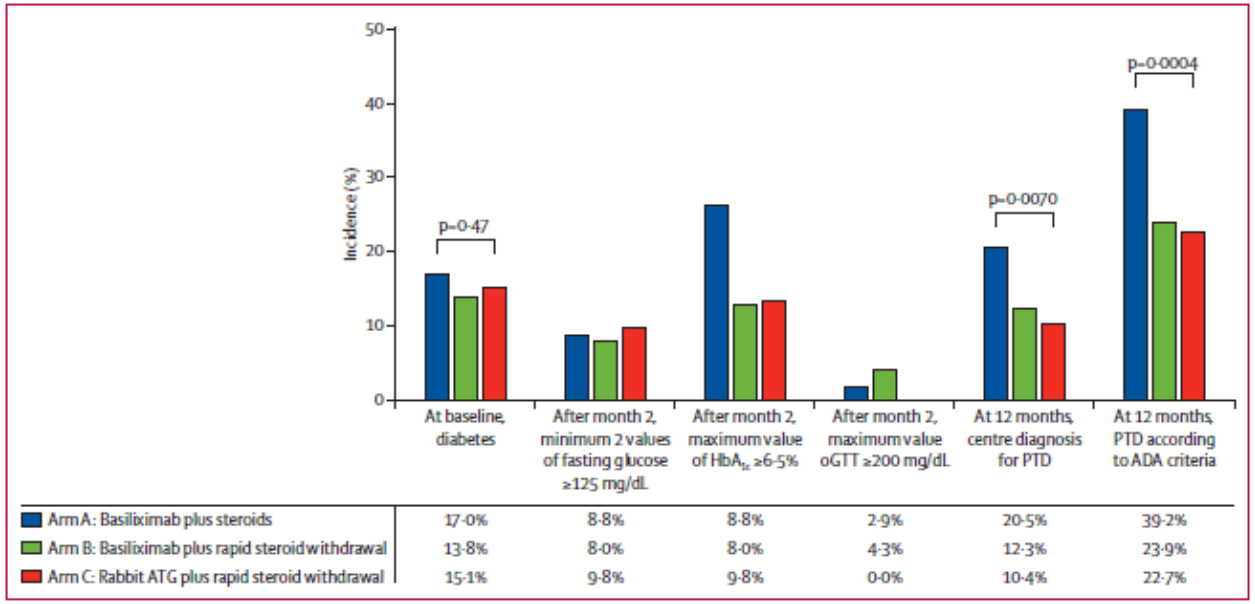
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Steroid avoidance versus steroid maintenance				
Mortality Follow-up: 1 year	31 per 1000	30 per 1000 (16 to 56)	**RR 0.96** (0.52 to 1.8)	1462 (10)	⊕⊕◯◯ **low** [1,2]	
Graft loss (excluding death) Follow-up: 1 year	42 per 1000	46 per 1000 (27 to 79)	**RR 1.09** (0.64 to 1.86)	1211 (7)	⊕⊕◯◯ **low** [2,3]	
Acute rejection Follow-up: 1 year	204 per 1000	323 per 1000 (221 to 470)	**RR 1.58** (1.08 to 2.3)	835 (7)	⊕⊕⊕◯ **moderate** [4]	
NODAT Follow-up: 5 years	107 per 1000	80 per 1000 (54 to 117)	**RR 0.75** (0.51 to 1.1)	1618 (9)	⊕⊕◯◯ **low** [2,5]	
CMV Infection Follow-up: 5 years	106 per 1000	101 per 1000 (74 to 138)	**RR 0.96** (0.7 to 1.31)	1454 (6)	⊕⊕◯◯ **low** [2,6]	

Haller Cochrane Database Syst Rev 2016

Stéroïdes

A- Basiliximab / FK-MMF / MS
B- Basiliximab / FK-MMF / SW (J8)
C- ATG / FK-MMF / SW (J8)





Thomusch Lancet 2016

Stéroïdes

Après transplantation

9 études
1439 participants

Steroid withdrawal versus steroid maintenance for kidney transplant recipients

Patient or population: kidney transplant recipients
Intervention: steroid withdrawal
Comparison: steroid maintenance

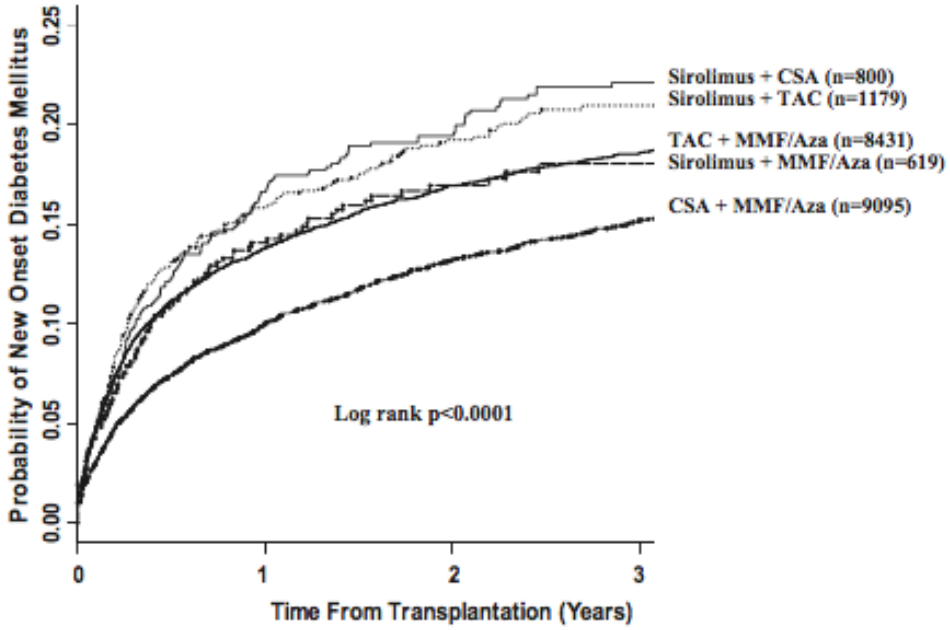
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Steroid maintenance	Steroid withdrawal			
Mortality Follow-up: 1 year	**22 per 1000**	**15 per 1000** (8 to 29)	**RR 0.68** (0.36 to 1.3)	1913 (10)	⊕⊕⊝⊝ **low** [1,2]
Graft loss (excluding death) Follow-up: 1 year	**32 per 1000**	**38 per 1000** (23 to 62)	**RR 1.17** (0.72 to 1.92)	1817 (8)	⊕⊕⊝⊝ **low** [2,3]
Acute rejection Follow-up: 1 year	**152 per 1000**	**268 per 1000** (182 to 396)	**RR 1.77** (1.2 to 2.61)	1913 (10)	⊕⊕⊕⊝ **moderate** [1]
NODAT Follow-up: 5 years	**57 per 1000**	**44 per 1000** (28 to 69)	**RR 0.77** (0.49 to 1.21)	1439 (6)	⊕⊕⊝⊝ **low** [2,4]
CMV infection Follow-up: 5 years	**100 per 1000**	**104 per 1000** (80 to 137)	**RR 1.04** (0.8 to 1.36)	1758 (5)	⊕⊕⊝⊝ **low** [2,5]

Haller Cochrane Database Syst Rev 2016

Inhibiteurs de mTOR

Factor	HR	95% CI	P
Drug combination throughout first transplantation year			
CSA + MMF/Aza	1.00		
TAC + MMF/Aza	1.40	1.28 to 1.54	<0.0001
Sirolimus + MMF/Aza	1.14	0.80 to 1.61	0.4600
Sirolimus + CSA	1.78	1.44 to 2.21	<0.0001
Sirolimus + TAC	1.76	1.44 to 2.16	<0.0001

USRDS
20154 1ères TR
Non diabétiques



Johnston J Am Soc Nephrol 2008

Inhibiteurs de mTOR

Après transplantation

	Group 1 (n = 26)		Group 2 (n = 15)		Controls (n = 70)
	CsA	SRL	TAC+SRL (low-dose)	SRL (full dose)	
AUC glucose (mmol/L)	15.63 ± 3.67	16.21 ± 3.54	15.70 ± 1.61	17.43 ± 3.49[b]	12.71 ± 2.8
AUC insulin (pmol/L)	1225.70 ± 660.09	1199.13 ± 594.26	726.60 ± 346.13	788.96 ± 671.20	707.62 ± 310.74
AUC C-peptide (nmol/L)	5.57 ± 3.12	6.31 ± 2.63[b]	4.20 ± 1.88	6.17 ± 2.97[c]	—
Secretory AUC	77.22 ± 35.95	72.69 ± 28.24	46.96 ± 22.72	47.27 ± 39.06	55.98 ± 24.07
First-phase insulin release (pmol/L)	1949.36 ± 797.48	1838.38 ± 671.23	1193.22 ± 585.42	1042.62 ± 851.44	1322.02 ± 397.61
Second-phase insulin release (pmol/L)	523.25 ± 189.22	484.59 ± 169.55	327.51 ± 141.83	293.94 ± 205.07	348.95 ± 96.51
DI	100.70 ± 101.23	76.06 ± 101.62[c]	102.52 ± 45.17	63.98 ± 57.12[d]	114.77 ± 35.14
MCR (ml/kg per min)	6.77 ± 3.82	6.08 ± 3.95[c]	9.16 ± 1.28	7.82 ± 2.23[c]	9.07 ± 1.58

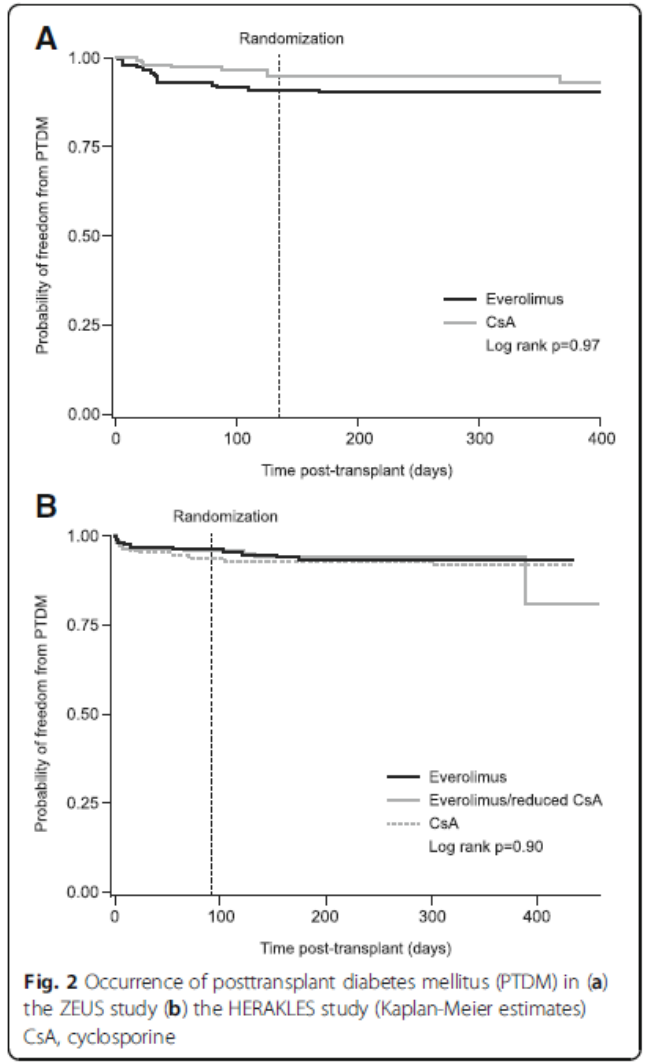


Fig. 2 Occurrence of posttransplant diabetes mellitus (PTDM) in (**a**) the ZEUS study (**b**) the HERAKLES study (Kaplan-Meier estimates) CsA, cyclosporine

Teutonico J Am Soc Nephrol 2005
Sommerer BMC Nephrol 2018

Belatacept

Studies included in data synthesis: 4 (1516 participants)

BENEFIT Study 2008
BENEFIT-EXT 2009
Ferguson 2010
Vincenti 2005

CNI : CsA très majoritaire
Minimise le bénéfice pour le PTDM
Minimise l'excès de rejet aigu

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CNI	Belatacept				
New onset diabetes	67.2 per 1000	50.0 per 1000 (26.9 to 62.5)	0.61 (0.40 to 0.93)	1049 (4)	Moderate quality	
Acute rejection	164.7 per 1000	257.0 per 1000 (140.0 to 471.0)	1.56 (0.85 to 2.86)	1516 (4)	High quality	

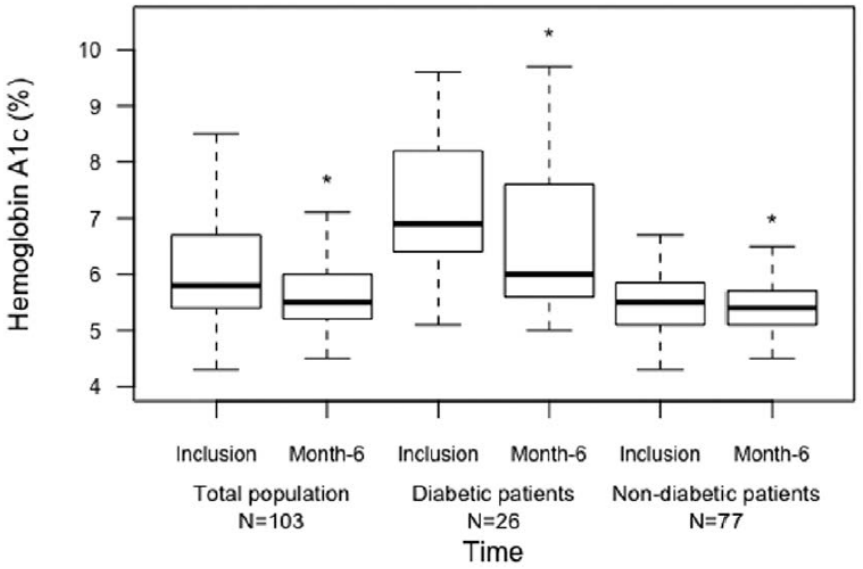
Masson Cochrane Database Syst Rev 2014

Belatacept

Après transplantation

Diabetes treatment at baseline and 6 mo after the introduction of belatacept (n = 26)

	Baseline	M6	*P*
Insulin therapy regimen			
Basal insulin, n (%)	13 (50)	13 (50)	1.00
Basal insulin units (UI)	17 ± 20	16 ± 19	1.00
Fast insulin, n (%)	10 (38)	6 (23)	0.09
OAD regimen			
Total OAD, n (%)	20 (76)	18 (69)	0.52
>1 OAD, n (%)	13 (50)	11 (42)	0.78
Metformin, n (%)	7 (26)	7 (26)	1.00
DPP4 inhibitors, n (%)	15 (58)	13 (50)	0.58
Glinides, n (%)	6 (23)	5 (19)	1.00
Sulfamides, n (%)	5 (19)	5 (19)	1.00
GLP-1 analogs, n (%)	2 (8)	2 (8)	1.00



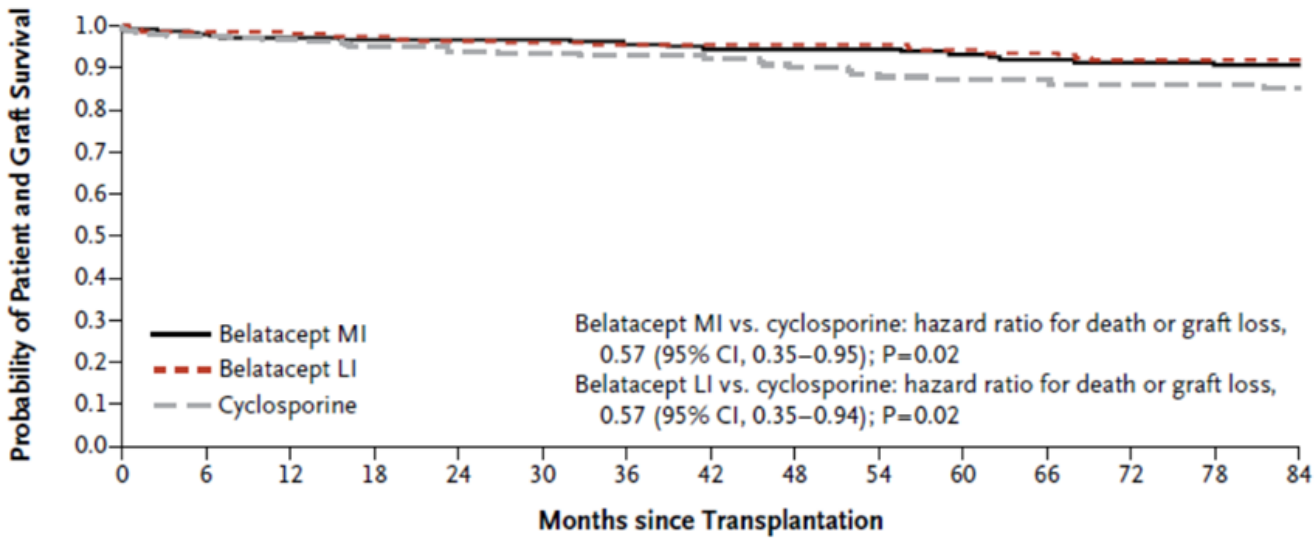
Conclusions

Il y a peu de preuves que la modification de l'IS modifie :

- Le contrôle du diabète
- Le risque associé au diabète

Le choix de l'IS est guidé par le bénéfice de survie du transplant et du patient

5. Choose immunosuppression regimens so as to achieve the best outcome for patient and graft survival, irrespective of PTDM risk.



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Ne pas oublier que le traitement du diabète (y compris après transplantation), ce sont …