ABCD and Renal Association meeting, Birmingham 2019

Post-transplantation diabetes

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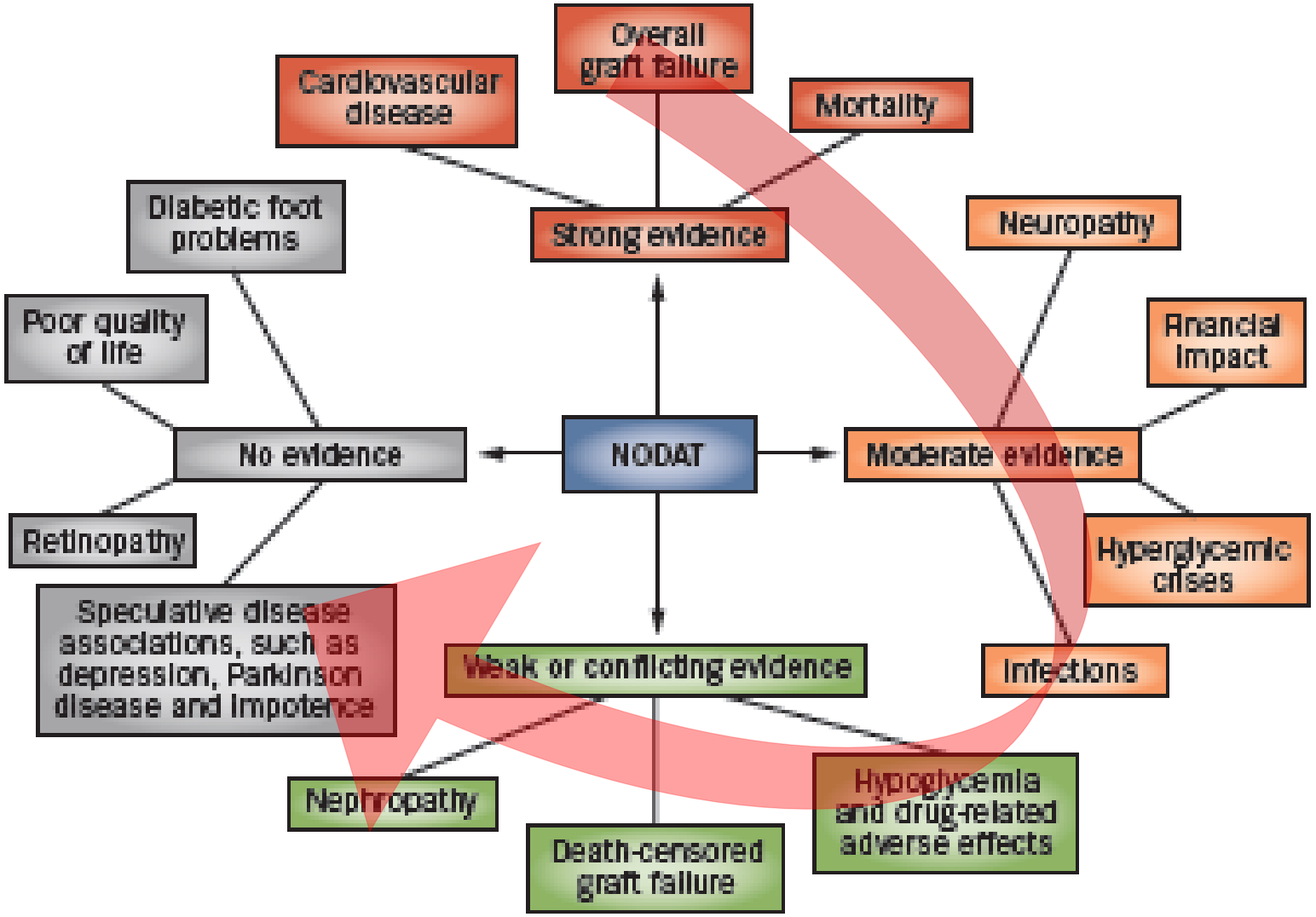
Disclosures
Advisory Board: Boehringer Ingelheim/Lilly, Sandoz, Astellas
Grant funding: Chiesi
Travel reimbursement: Sandoz, Novartis

Overview

- Clinical outcomes and PTDM
- Risk factors and pathophysiology for PTDM
- Diagnosis of PTDM
- Prevention and management of PTDM
  - Modifying risk factors (e.g. immunosuppression)
  - Intervention
- Research in progress
- Outcomes from the CAVIAR study
- Summary and conclusion

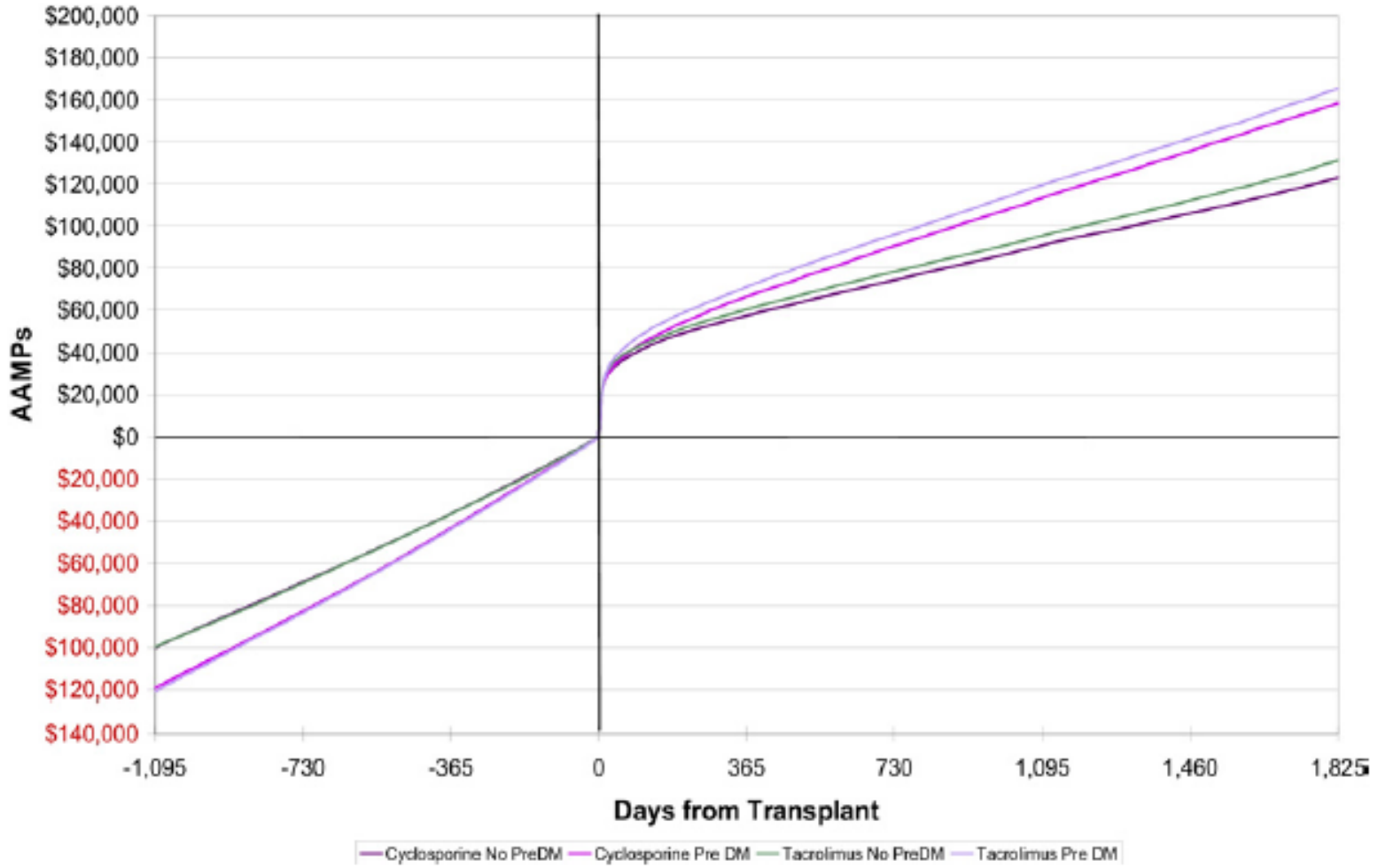
Clinical outcomes and PTDM

Complications associated with PTDM



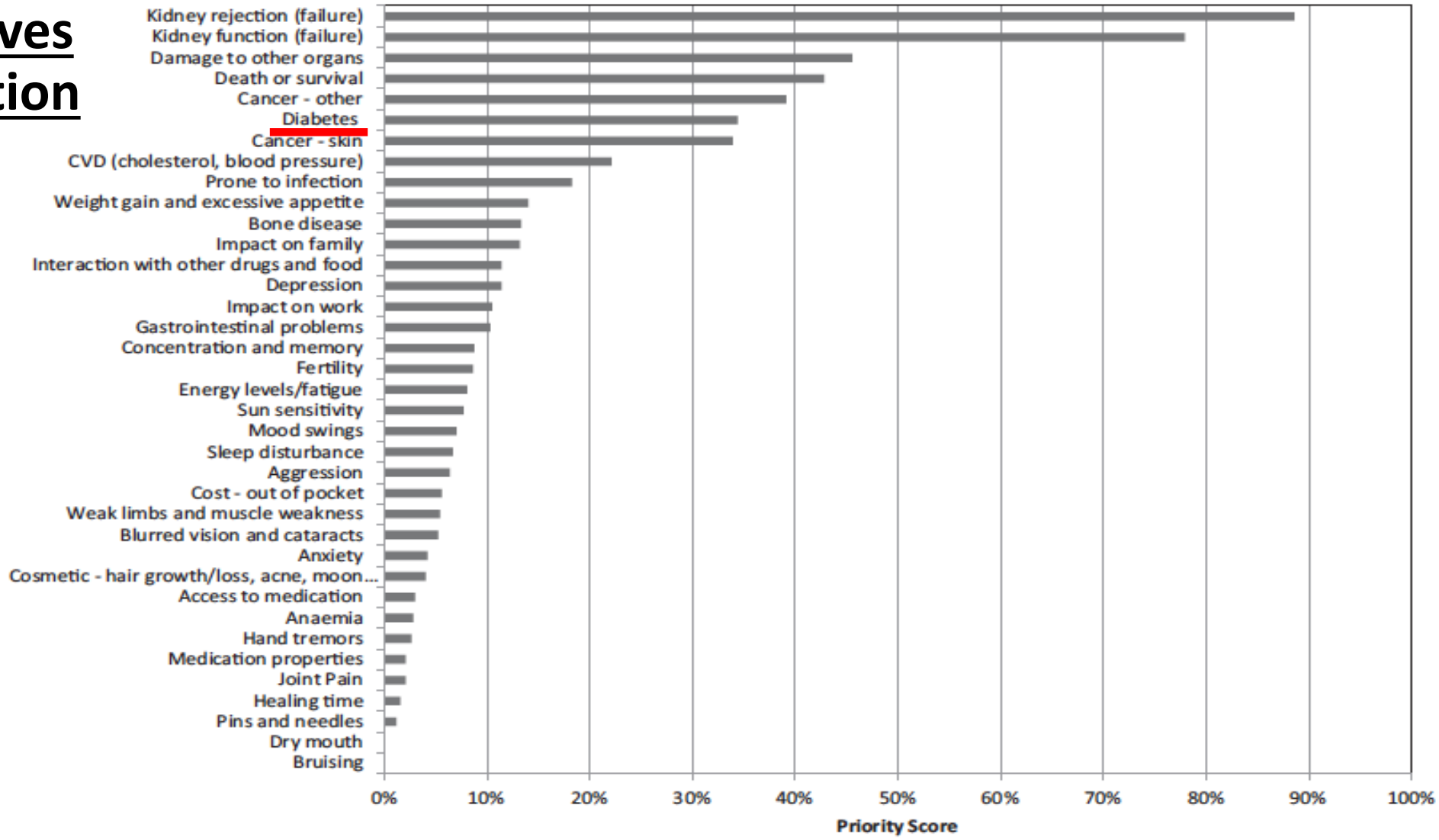
Sharif A, Baboolal K. Nat Rev Nephrol 2012

PTDM adds significant cost to post-transplant care



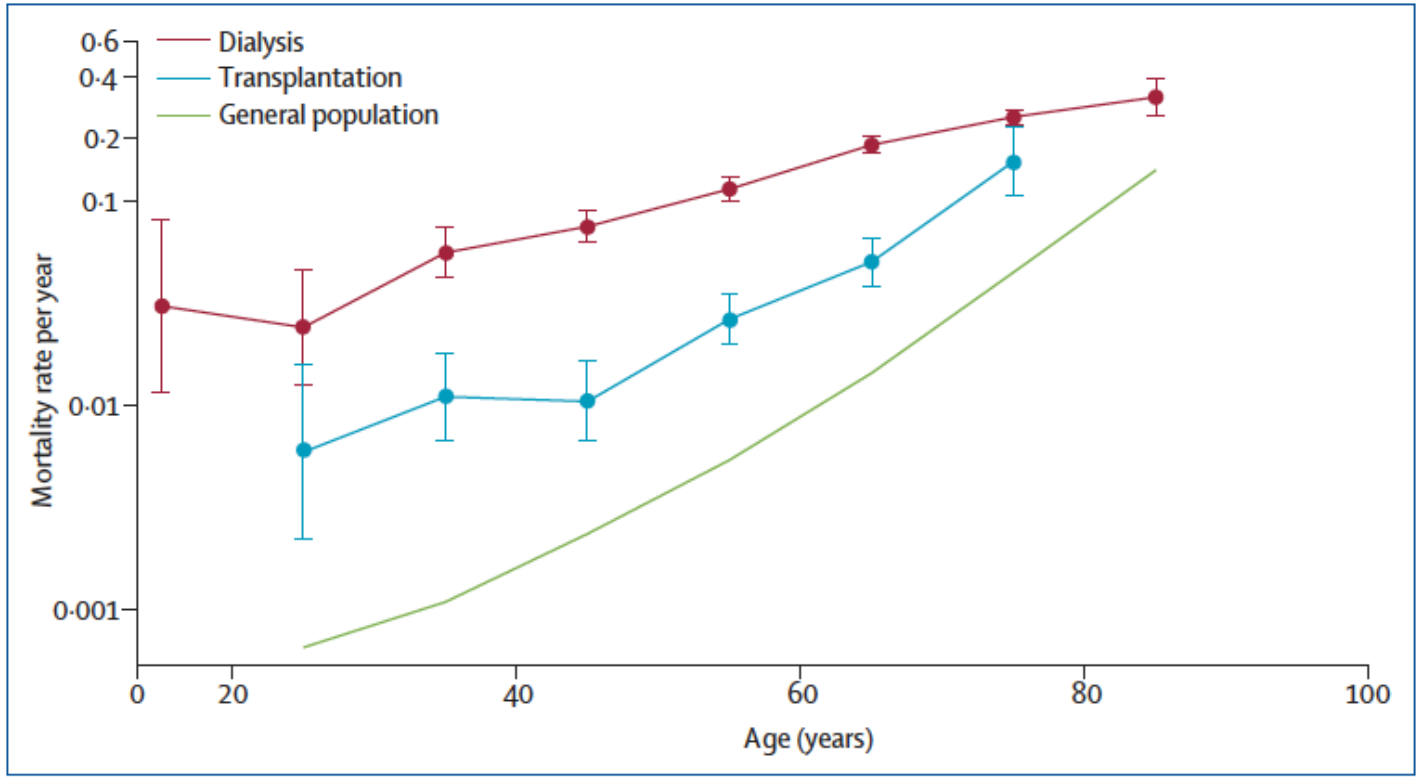
Woodward et al. Value in Health 2011

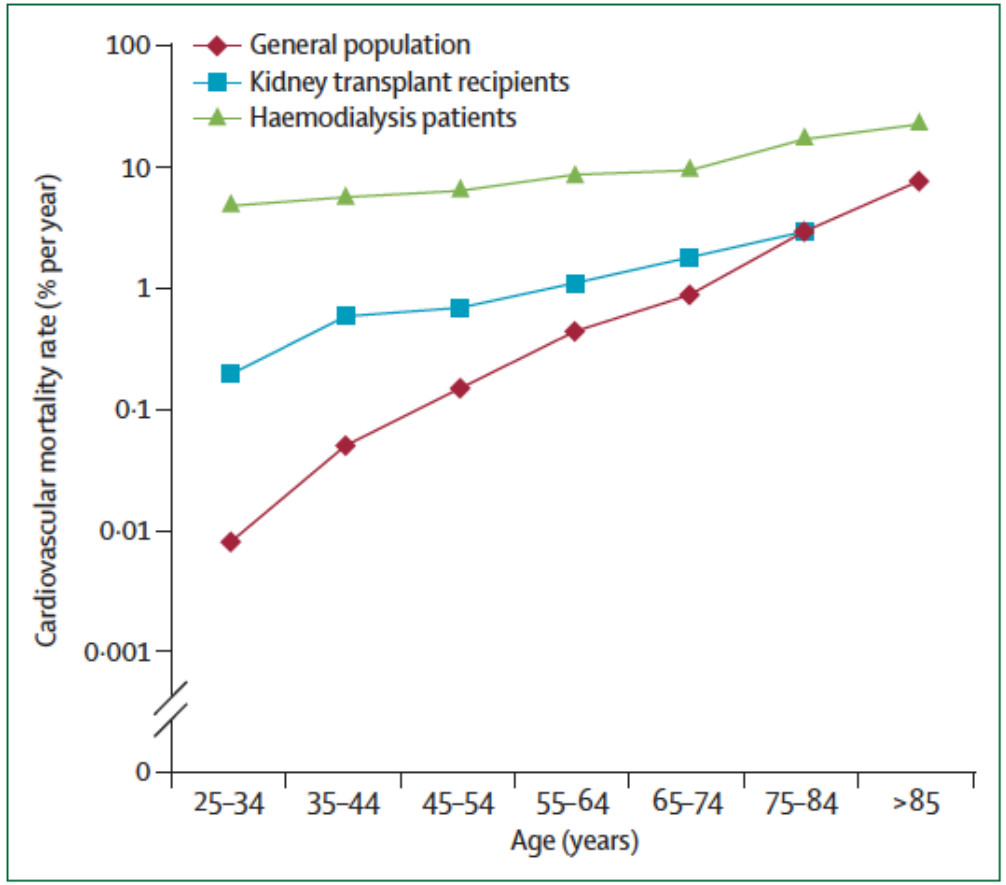
Patient perspectives after transplantation



Howell et al. AJKD 2012

Kidney transplantation reduces all-cause and cardiovascular-related mortality for dialysis patients

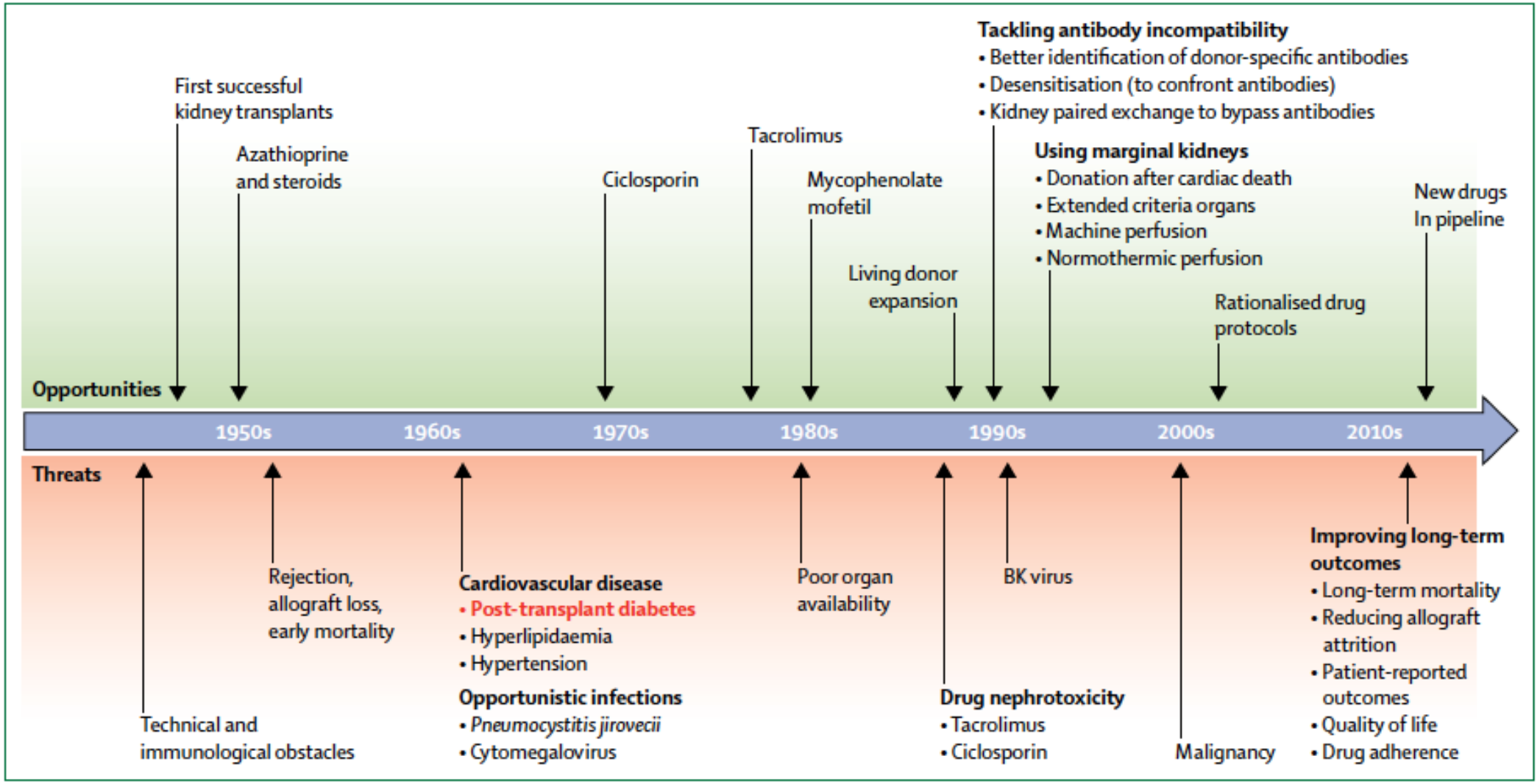




Chapman JR. Lancet 2011

Jardine et al. Lancet 2011

PTDM in the context of competing risks after kidney transplantation



Sharif A, Cohney S. Lancet Diab Endocrinol 2016

Risk factors and pathophysiology for PTDM

Identifying patients at risk for PTDM

Non-modifiable

- Age
- Male sex?
- Deceased-donor kidney?
- Genetic
- HLA matching
- Non-Caucasian ethnicity
- Family history of diabetes
- Gestational diabetes
- ADPKD?
- Hepatitis C

Modifiable

- Obesity/Weight gain
- Metabolic syndrome
- CMV infection post-transplant
- Glucose intolerance
- Anti-hypertensives
- Uric acid/Mg abnormality post-transplant
- Immunosuppression

Sharif A, Baboolal K. Nat Rev Nephrol 2010; 6: 415-423
Sharif A. Curr Opin Nephrol Hypertens 2012; 21: 574-9

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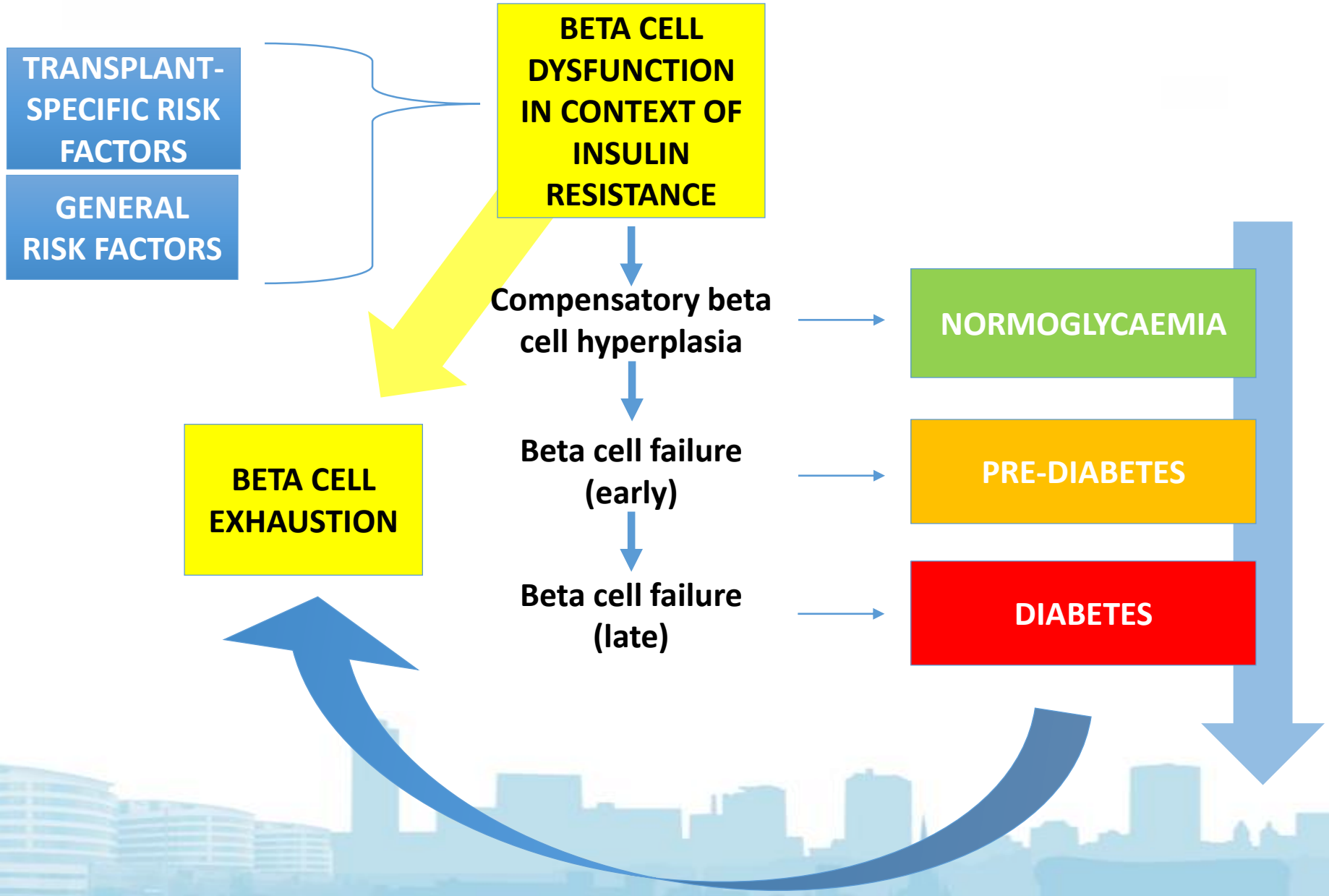
Pathophysiology of PTDM



Diagnosis of PTDM

A brief evolution of PTDM diagnosis

FPG – fasting plasma glucose
2HPG – 2-hour plasma glucose

Study	N	Definition	NODAT incidence (%) Months post 1	6	Years post 1	3	5	10	15
Cosio et al. (2001) (Ref. 5)	2078	Treatment past day 30			7	10	13	21	30
Kasiske et al. (2003) (Ref. 4)	11 659	Medicare claim	9		16	24			
Vincenti et al. (2008) (Ref. 6)	567	Treatment past day 30		13					
Luan et al. (2011) (Ref. 7)	25 837	Registry				16			

Study	N	Definition	NODAT incidence (%) Months post 1	2	3	6	Years post 1	4	6	7
Hagen et al. (2003) (Ref. 9)	63	OGTT		19				22		
David-Neto et al. (2007) (Ref. 10)	84	OGTT	14	18		19	9			
Hur et al. (2007) (Ref. 11)	77	OGTT					39			35
Porrini et al. (2008) (Ref. 12)	154	OGTT			31		20			
Valderhaug et al. (2009) (Ref. 13)	1637	OGTT		17[2]						
Luan et al. (2010) (Ref. 14)	591	FBG						15[1]		

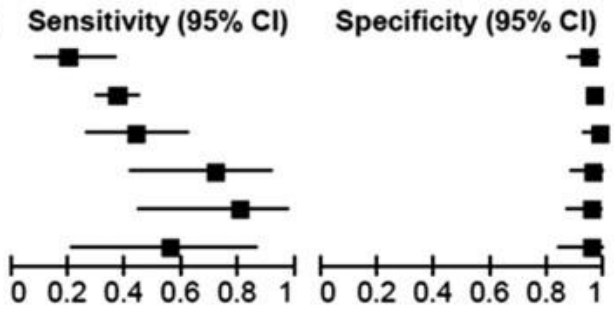
Status	PTM (and pre-diabetes) criteria
Diabetes	• Symptoms of diabetes plus 11.1 mmol/L OR **A1c ≥ 48 mmol/mol** • FPG ≥ 7.0 mmol/L • 2HPG ≥ 11.1 mmol/L during OGTT
Impaired fasting glucose	• FPG 5.6-6.9 mmol/L
Impaired glucose tolerance	• FPG < 7.0 mmol/L • 2HPG 7.8-11.0 mmol/L
Normal glucose tolerance	• FPG < 5.6 mmol/L **A1c < 42 mmol/mol** • 2HPG < 7.8mmol/L

Yates et al. AJT 2012

HbA1c for PTDM diagnosis: high specificity but low-moderate sensitivity

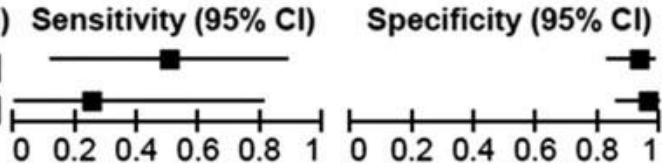
A

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Clayton 2015	7	5	28	79	0,20 [0,08, 0,37]	0,94 [0,87, 0,98]
Eide 2015	61	57	103	1391	0,37 [0,30, 0,45]	0,96 [0,95, 0,97]
Pimentel 2015	14	2	18	88	0,44 [0,26, 0,62]	0,98 [0,92, 1,00]
Rosetteinstein 2016	10	3	4	66	0,71 [0,42, 0,92]	0,96 [0,88, 0,99]
Shabir 2013	8	3	2	58	0,80 [0,44, 0,97]	0,95 [0,86, 0,99]
Yates 2013	5	2	4	39	0,56 [0,21, 0,86]	0,95 [0,83, 0,99]



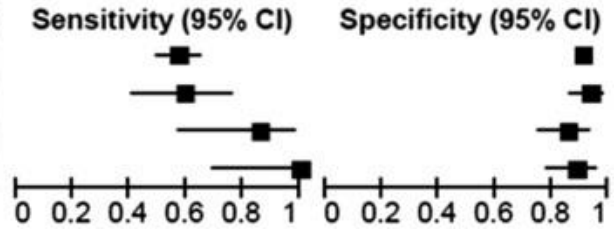
B

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Shabir 2013	3	4	3	51	0,50 [0,12, 0,88]	0,93 [0,82, 0,98]
Yates 2013	1	2	3	45	0,25 [0,01, 0,81]	0,96 [0,85, 0,99]



C

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Eide 2015	94	134	70	1314	0,57 [0,49, 0,65]	0,91 [0,89, 0,92]
Pimentel 2015	19	6	13	84	0,59 [0,41, 0,76]	0,93 [0,86, 0,98]
Rosetteinstein 2016	12	10	2	59	0,86 [0,57, 0,98]	0,86 [0,75, 0,93]
Shabir 2013	10	7	0	54	1,00 [0,69, 1,00]	0,89 [0,78, 0,95]



Forest plots of estimates of sensitivity and specificity in each study.:

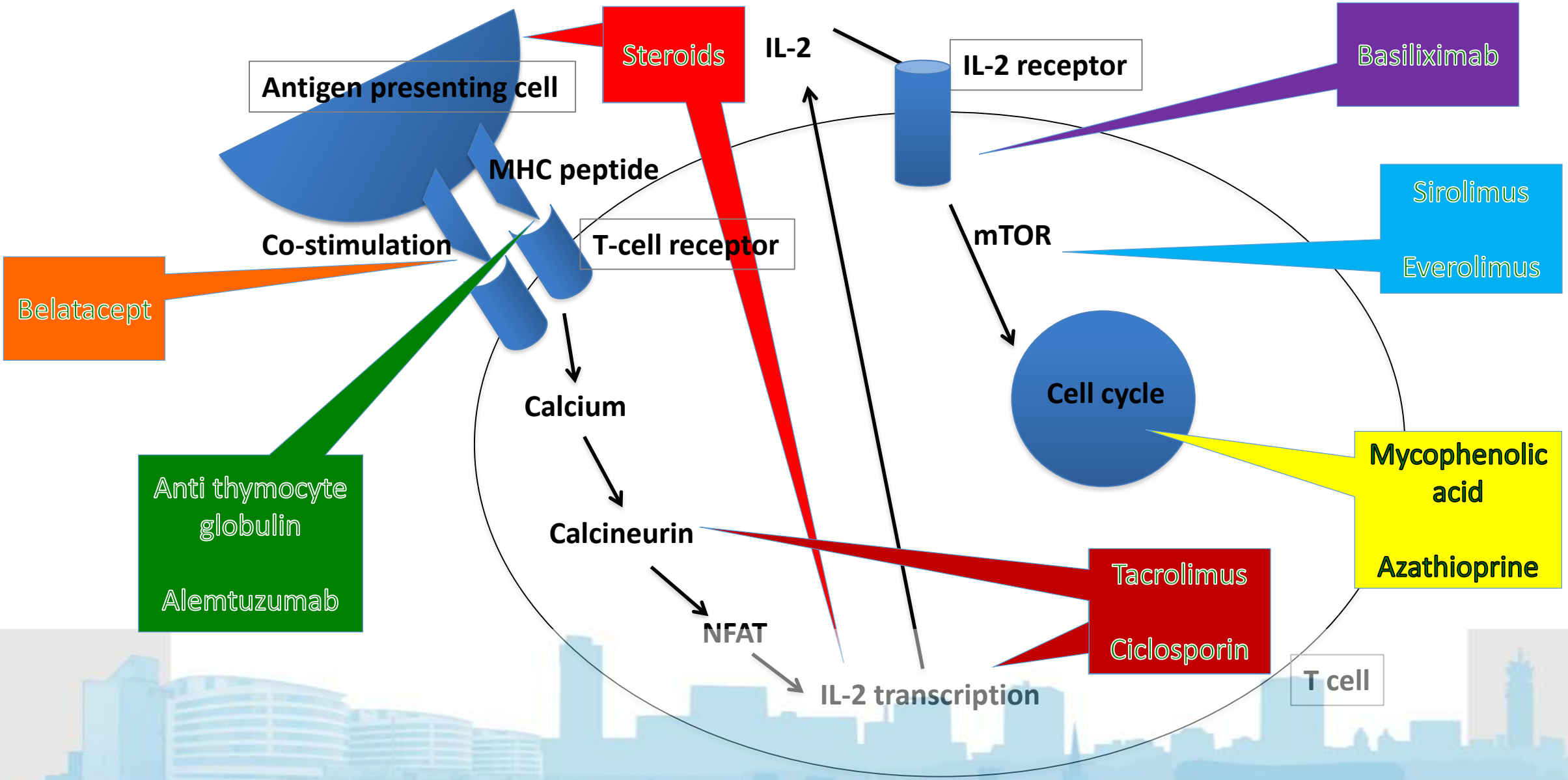
- ***A) HbA1c6.5% in the initial months after renal transplantation;***
- ***B) HbA1c6.5% at 12 months after renal transplantation;***
- ***C) HbA1c6.2% in the initial months after renal transplantation.***

Pimental et al. NDT 2017

Prevention and management of PTDM

Modifying risk factors

Burgeoning armamentarium of immunosuppression



Cardio-metabolic side effects of contemporary immunosuppression

	Post-transplant diabetes	Lipids	Blood pressure	GFR	Proteinuria	Weight gain
Corticosteroids*	Increased	Increased	Increased	--	--	Greatly increased
Tacrolimus*	Increased	Slightly increased	Increased	Slightly decreased	--	--
Ciclosporin*	Slightly increased	Increased	Greatly increased	Slightly decreased	--	--
mTORi*	Slightly increased	Greatly increased	--	--	Slightly increased	--
Mycophenolic acid*	--	--	--	--	--	--
Azathioprine*	--	--	--	--	--	--
Belatacept*	Slightly decreased?	Slightly decreased?	Slightly decreased?	--	--	--
Basiliximab†	Slightly increased?	--	--	--	--	--
Monoclonals†	--	--	--	--	--	--

GFR=estimated glomerular filtration rate. *Maintenance immunosuppression. †Induction therapy. ? indicates insufficient evidence.

Sharif and Cohney. Lancet Diab Endo 2016

Post-transplant diabetes management

Should we alter immunosuppression?

- Selection of an appropriate immunosuppressive regimen must be considered carefully for each individual patient
- Because there is evidence that some immunosuppressant therapies are more diabetogenic than others, selection of an appropriate immunosuppressive regimen should be considered, taking into account the individual's diabetes and CVD risk profile, the relative diabetogenicity and risk for diabetes of each immunosuppressant, and the efficacy of each agent.

Davidson et al. Transplantation 2003

- Recommendation 5: Choose and Use Immunosuppression Regimens Shown to Have the Best Outcome for Patient and Graft Survival, Irrespective of PTDM Risk

Sharif et al. AJT 2014

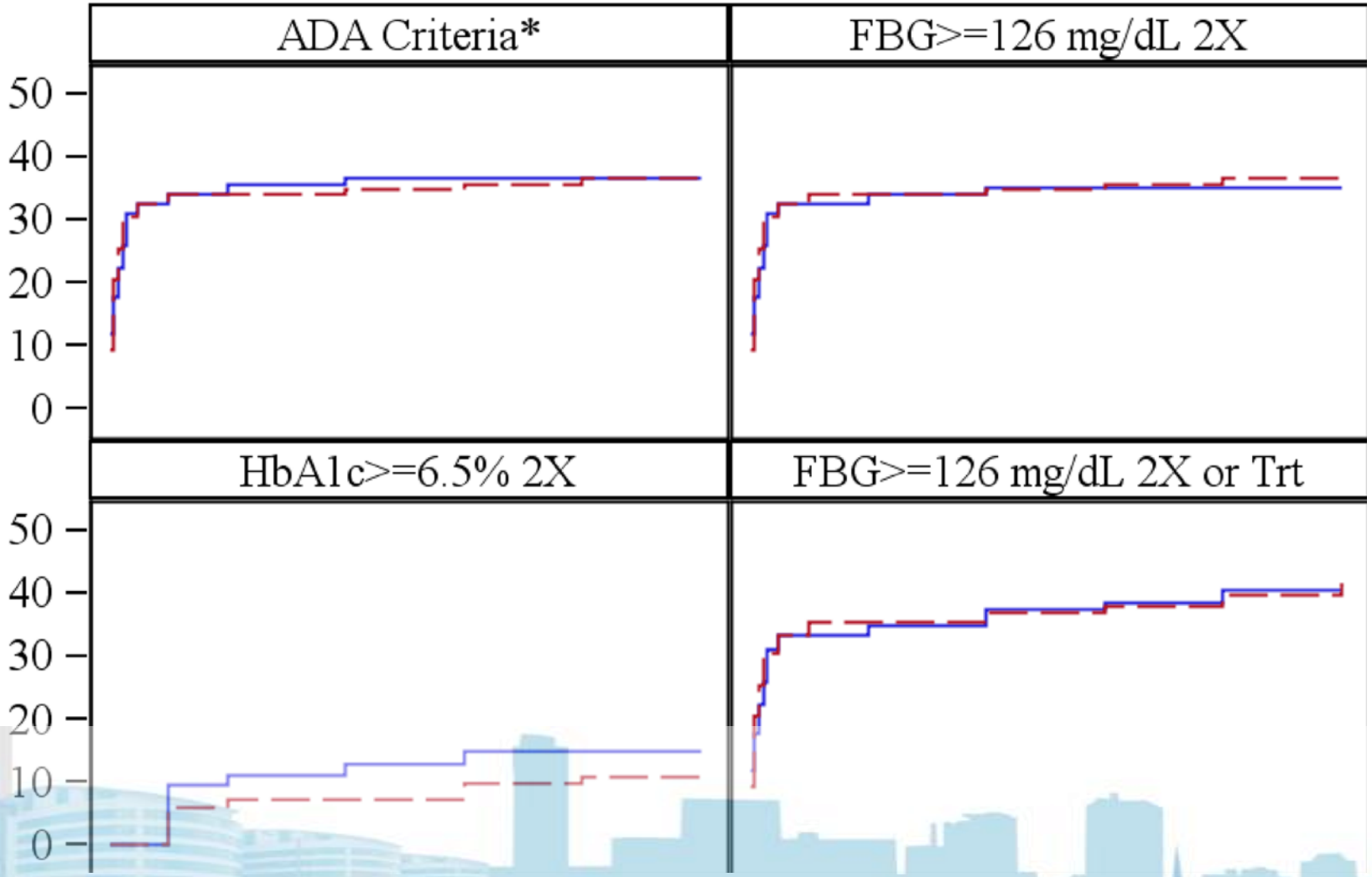
Steroid avoidance or early withdrawal: meta-analysis

- Systematic review and meta-analysis of 34 randomised controlled studies (n=5637 renal transplant recipients)

- Steroid avoidance/early withdrawal associated with:
  - No significant difference in patient/graft survival
  - Increase risk for rejection
  - Worse graft function
  - Improved cardiovascular risk profile:
    - Less hypertension (RR 0.90 [95% CI 0.85-0.94])
    - Less hypercholesterolaemia (RR 0.76 [95% CI 0.67-0.87])
    - Less PTDM (RR 0.64 [95% CI 0.50-0.83])

Knight et al. Transplantation 2010

Astellas Corticosteroid Withdrawal Study Group – 5-year PTDM data



Continued maintenance corticosteroids

Corticosteroid withdrawal (day 7)

Pirsch et al. Am J Transplant 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

Henrik Ekberg, M.D., Ph.D., Helio Tedesco-Silva, M.D., Alper Demirbas, M.D., Štefan Vítko, M.D., Björn Nashan, M.D., Ph.D., Alp Gürkan, M.D., F.A.C.S., Raimund Margreiter, M.D., Christian Hugo, M.D., Josep M. Grinyó, M.D., Ulrich Frei, M.D., Yves Vanrenterghem, M.D., Ph.D., Pierre Daloze, M.D., and Philip F. Halloran, M.D., Ph.D., for the ELITE–Symphony Study*

Table 2. Primary End Point and Selected Secondary End Points.*

End Point	Standard-Dose Cyclosporine (N=390)	Low-Dose Cyclosporine (N=399)	Low-Dose Tacrolimus (N=401)	Low-Dose Sirolimus (N=399)	P Value†
Primary end point					
Mean calculated GFR — ml/min‡	57.1±25.1	59.4±25.1	65.4±27.0	56.7±26.9	<0.001
P value for comparison with tacrolimus	<0.001	0.001	Reference	<0.001	
Secondary end points					
Mean measured GFR — ml/min§	63.5±25.4	65.3±26.6	69.6±27.9	64.4±28.5	0.04
P value for comparison with tacrolimus	0.01	0.10	Reference	0.02	
Mean calculated GFR — ml/min¶	46.2±23.1	50.2±23.1	54.3±23.9	47.5±26.1	<0.001
P value for comparison with tacrolimus	<0.001	0.007	Reference	<0.001	
Acute rejection‖					
At 6 mo					
Biopsy-proven (excluding borderline values) — %	24.0	21.9	11.3	35.3	<0.001
P value for comparison with tacrolimus	<0.001	<0.001	Reference	<0.001	
Allograft survival‖					
Censored for death of patients with functioning allograft — %	91.9	94.3	96.4	91.7	0.02
P value for comparison with tacrolimus	0.007	0.18	Reference	0.007	
Uncensored for death of patients with functioning allograft — %	89.3	93.1	94.2	89.3	0.02
P value for comparison with tacrolimus	0.01	0.56	Reference	0.01	

Ekberg et al. N Engl J Med 2008

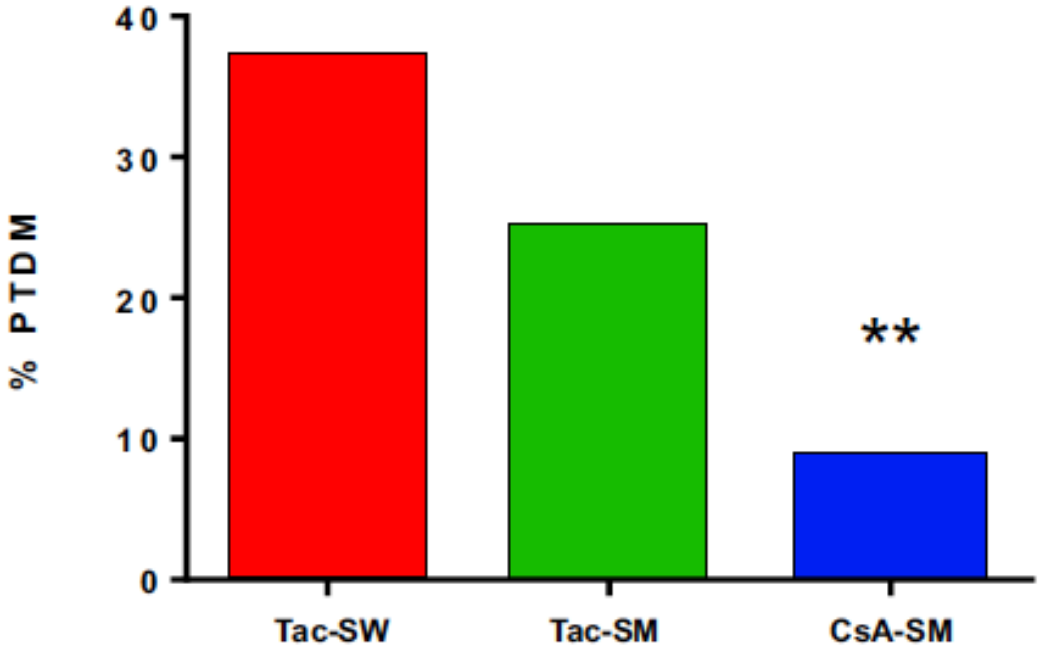
PTDM in Symphony study

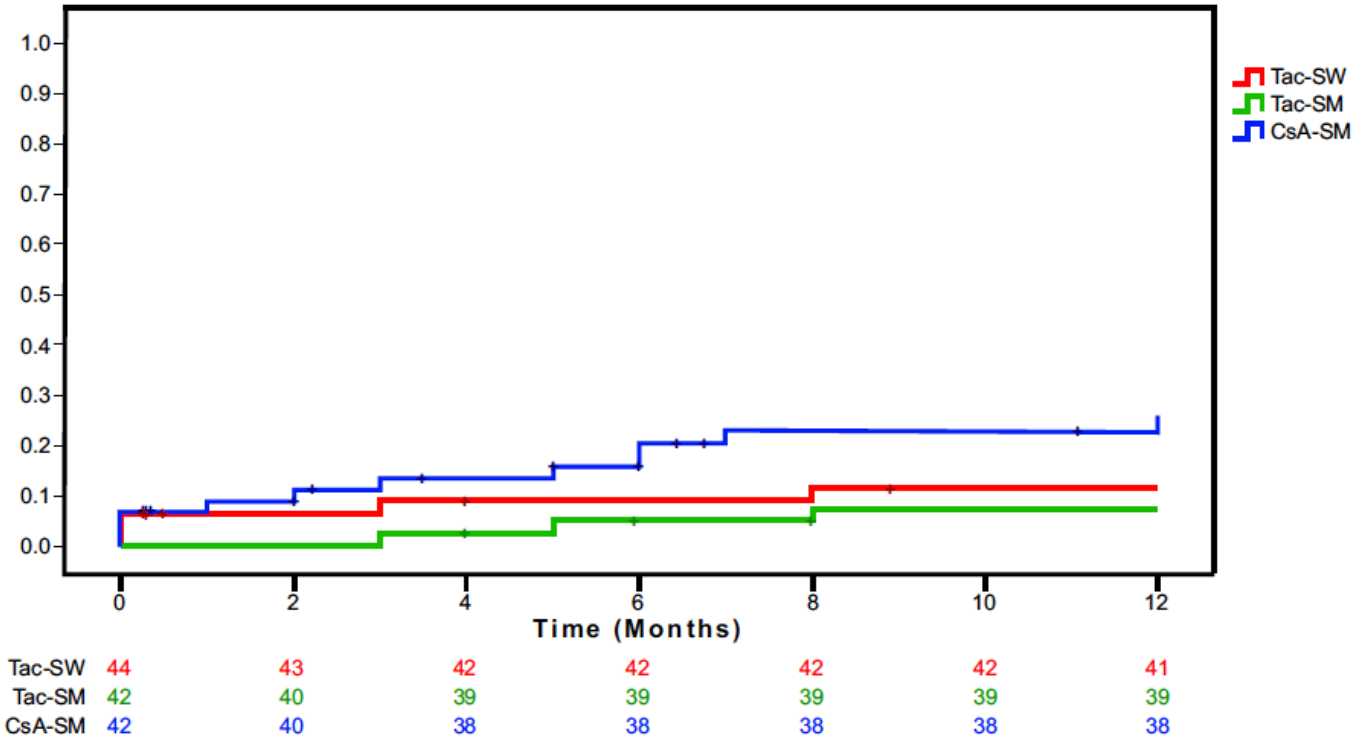
Event	Standard-dose CSA (n=384)	Low-dose CSA (n=408)	Low-dose TAC (n=403)	Low-dose sirolimus (n=380)
PTDM	6.4%	4.7%	10.6%	7.8%
Use of anti-diabetes meds	1.3%	1.5%	2.7%	1%

Ekberg et al. N Engl J Med 2008

KI REPORTS
KIReports.org
CLINICAL RESEARCH

Randomized Controlled Trial Assessing the Impact of Tacrolimus Versus Cyclosporine on the Incidence of Posttransplant Diabetes Mellitus





Torres et al. KI Reports 2019

Prospective randomized study of conversion from tacrolimus to cyclosporine A to improve glucose metabolism in patients with posttransplant diabetes mellitus after renal transplantation

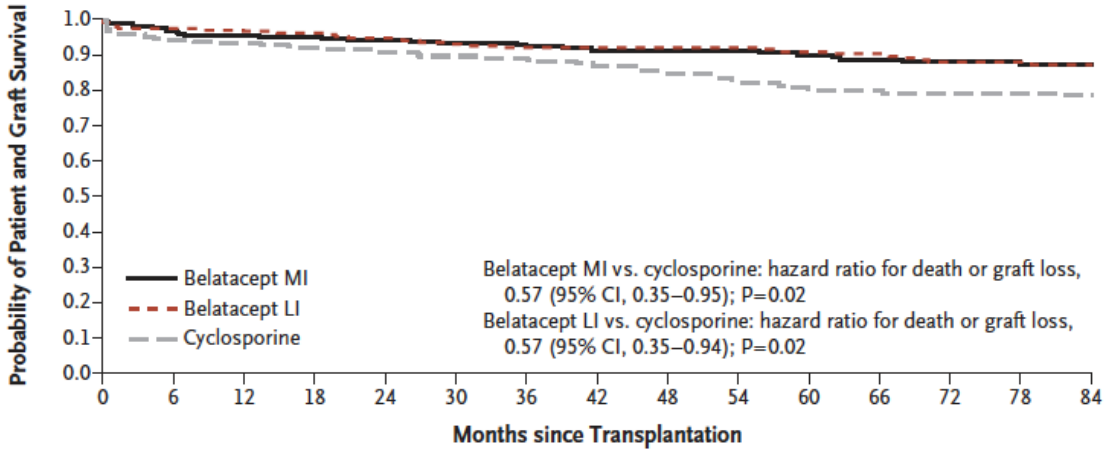
Karl M. Wissing[1] | Daniel Abramowicz[2] | Laurent Weekers[3] | Klemens Budde[4] | Thomas Rath[5] | Oliver Witzke[6] | Nilufer Broeders[7] | Mireille Kianda[8] | Dirk R. J. Kuypers[9]

(A)		Baseline	3 months	6 months	9 months	12 months	P[a]
Glycemia, mg/dL	CYC	125 ± 28	109 ± 33	111 ± 23	109 ± 26	120 ± 39	.06
	TAC	130 ± 45	132 ± 29	140 ± 38	138 ± 61	138 ± 47	
HbA_{1c}, %	CYC[b]	6.5 ± 0.9	6.1 ± 0.6	6.1 ± 0.6	6.2 ± 0.7	6.0 ± 0.9	.002
	TAC[b]	6.8 ± 0.8	6.7 ± 0.8	6.7 ± 0.9	6.8 ± 0.8	7.1 ± 1.7	

(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%)	
Patient without glucose-lowering therapy					
	CYC	9/16 (56%)	.045	13/16 (81%)	.55
	TAC	0/5 (0%)		3/5 (60%)	

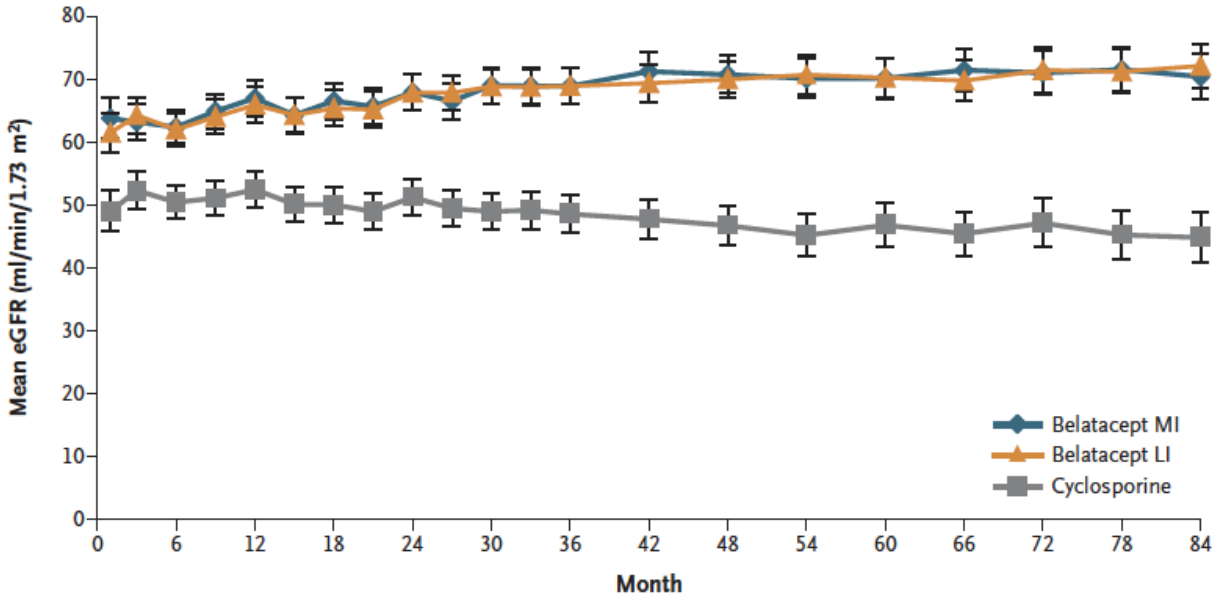
Wissing et al. AJT 2017

Belatacept: long-term data shows improved overall graft survival



No. at Risk

Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137
Cyclosporine	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92



Vincenti et al. NEJM 2016

Belatacept: improved cardio-metabolic profile

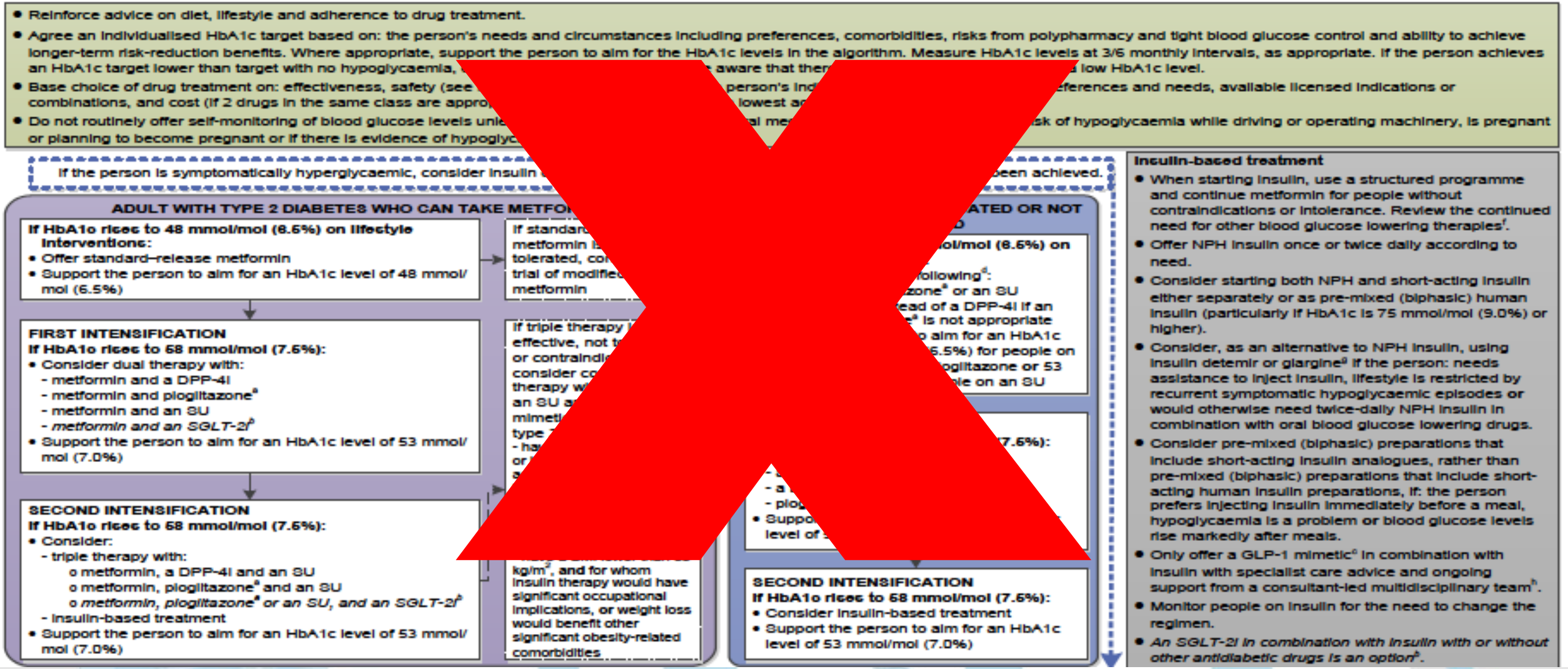
- Belatacept-treated kidney transplant recipients had better **graft function** (measured glomerular filtration rate (GFR) (3 studies 1083 recipients): 10.89 mL/min/1.73 m², 95% CI 4.01 to 17.77; estimated GFR (4 studies, 1083 recipients): MD 9.96 mL/min/1.73 m², 95% CI 3.28 to 16.64) than CNI-treated recipients.
- **Blood pressure** was lower (systolic (2 studies, 658 recipients): MD -7.51 mm Hg, 95% CI -10.57 to -4.46; diastolic (2 studies, 658 recipients): MD -3.07 mm Hg, 95% CI -4.83 to -1.31
- **Lipid profile** was better (non-HDL (3 studies 1101 recipients): MD -12.25 mg/dL, 95% CI -17.93 to -6.57; triglycerides (3 studies 1101 recipients): MD -24.09 mg/dL, 95% CI -44.55 to -3.64)
- Incidence of **new-onset diabetes after transplant** was reduced by 39% (4 studies (1049 recipients): RR 0.61, 95% CI 0.40 to 0.93) among belatacept-treated versus CNI-treated recipients.

Masson et al. Cochrane Data Syst Rev 2014

Prevention and management of PTDM

Intervention

NICE guidance [NG28]: December 2015 (updated April 2017)



http://www.nice.org.uk/guidance/ng28/resources

Advantages and disadvantages to glucose-lowering therapy in PTDM

	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

GLP-1=glucagon-like peptide 1. DPP-4=dipeptidase-4. CNI=calcineurin inhibitor. eGFR=estimated glomerular filtration rate. Adapted from British National Formulary.

Sharif and Cohney. Lancet Diab Endo 2016

Observational studies of anti-glycaemic drugs for management of PTDM

- Many small case series' published suggesting safety/efficacy:
  - Metformin
  - Repaglinide
  - Pioglitazone
  - DPP-4 inhibitors (vildagliptin, linagliptin, sitagliptin)
  - GLP-1 receptor agonist (liraglutide)
- Limited by inherent bias, small (carefully selected) samples, short follow up
- Non-randomised

American Journal of Transplantation 2014; 14: 115–123
Wiley Periodicals Inc.

doi: 10.1111/ajt.12518

Efficacy and Safety of Vildagliptin in New-Onset Diabetes After Kidney Transplantation—A Randomized, Double-Blind, Placebo-Controlled Trial

M. Haidinger[1], J. Werzowa[1], M. Hecking[1], M. Antlanger[1], G. Stemer[2], J. Pleiner[3], C. Kopecky[1], J. J. Kovarik[1], D. Döller[1], G. Pacini[4] and M. D. Säemann[1,*]

CLINICAL AND TRANSLATIONAL RESEARCH

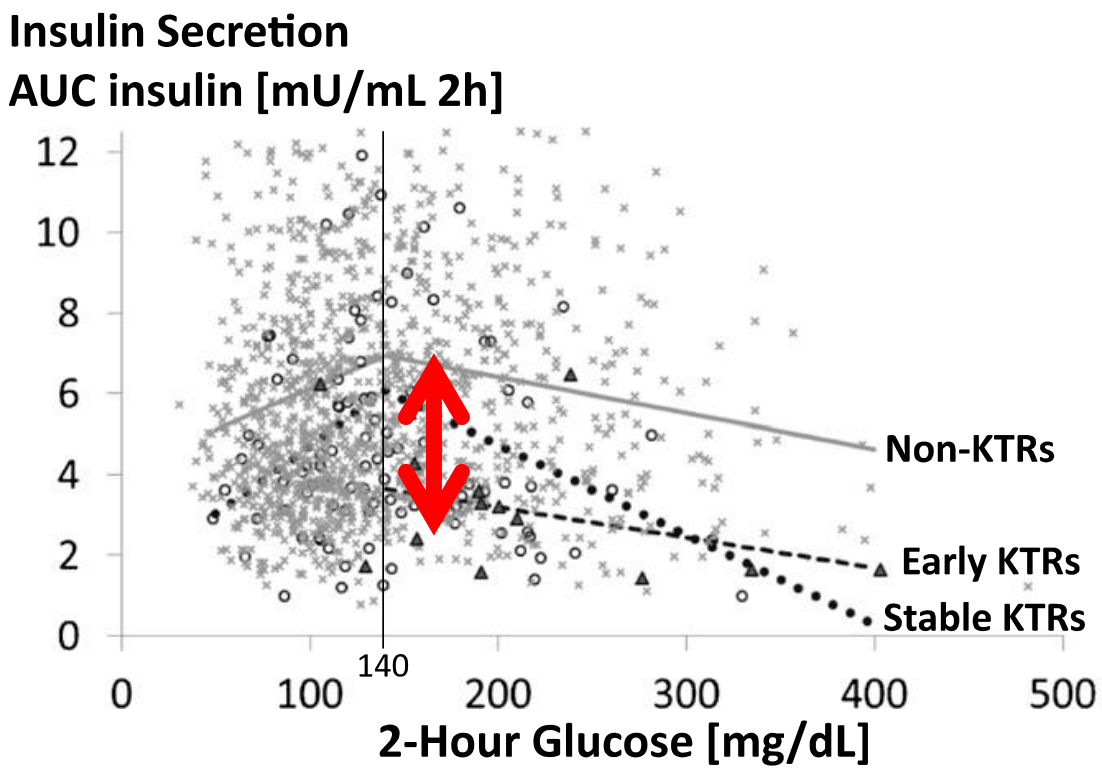
Vildagliptin and Pioglitazone in Patients With Impaired Glucose Tolerance After Kidney Transplantation: A Randomized, Placebo-Controlled Clinical Trial

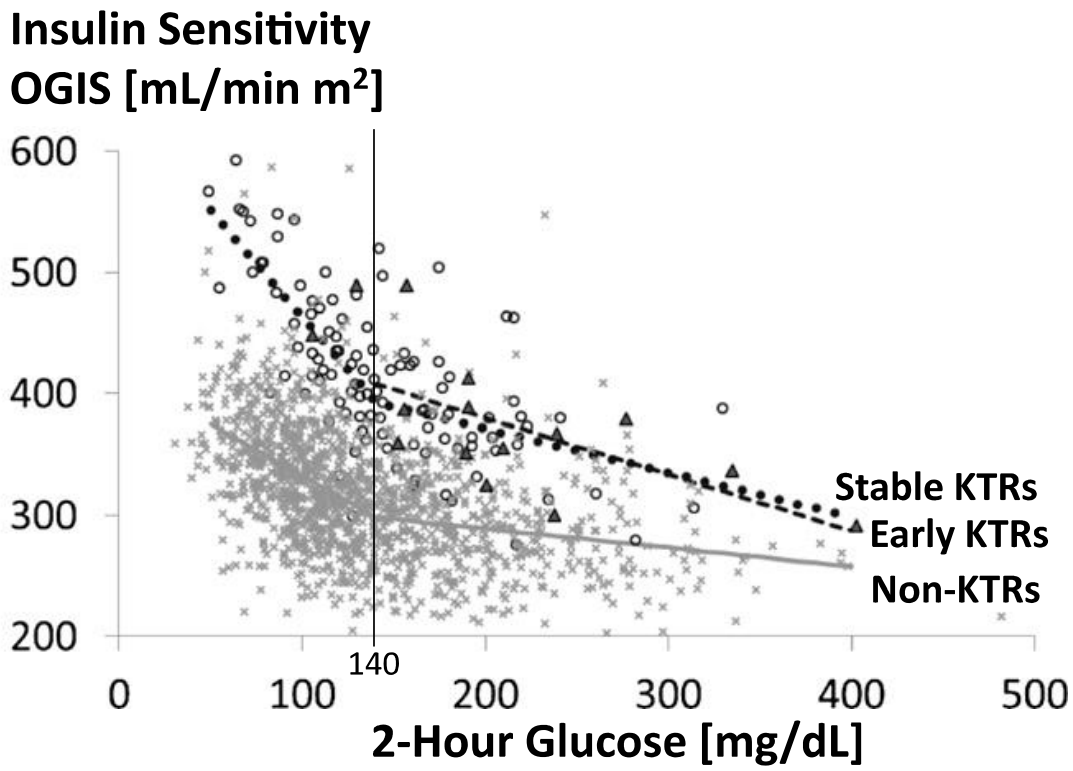
Johannes Werzowa,[1] Manfred Hecking,[1] Michael Haidinger,[1] Felix Lechner,[1] Dominik Döller,[1] Giovanni Pacini,[2] Gunar Stemer,[3] Johannes Pleiner,[4] Sophie Frantal,[5] and Marcus D. Säemann[1,6]

(*Transplantation* 2013;95: 456–462)

Beta-cell dysfunction is the key pathophysiological defect for early onset PTDM

Analysis of OGTT-Derived Measures: KTRs versus General Population





Hecking et al. Diabetes Care 2013

TIP: Study Design

Treat-to-target trial of Basal Insulin in Post Transplant Hyperglycemia
Efficacy and Safety of a Novel Protocol in Renal Transplant Recipients Receiving a Tacrolimus-based Immunosuppression

Inclusion: Tacrolimus, No history of DM, Informed Consent

Daily Measurements of Blood Glucose

(At least): Fasting, pre-lunch, pre-supper, post-supper

2 x 25 patients, Randomisation into 2 Study Arms

Arm A (treatment):

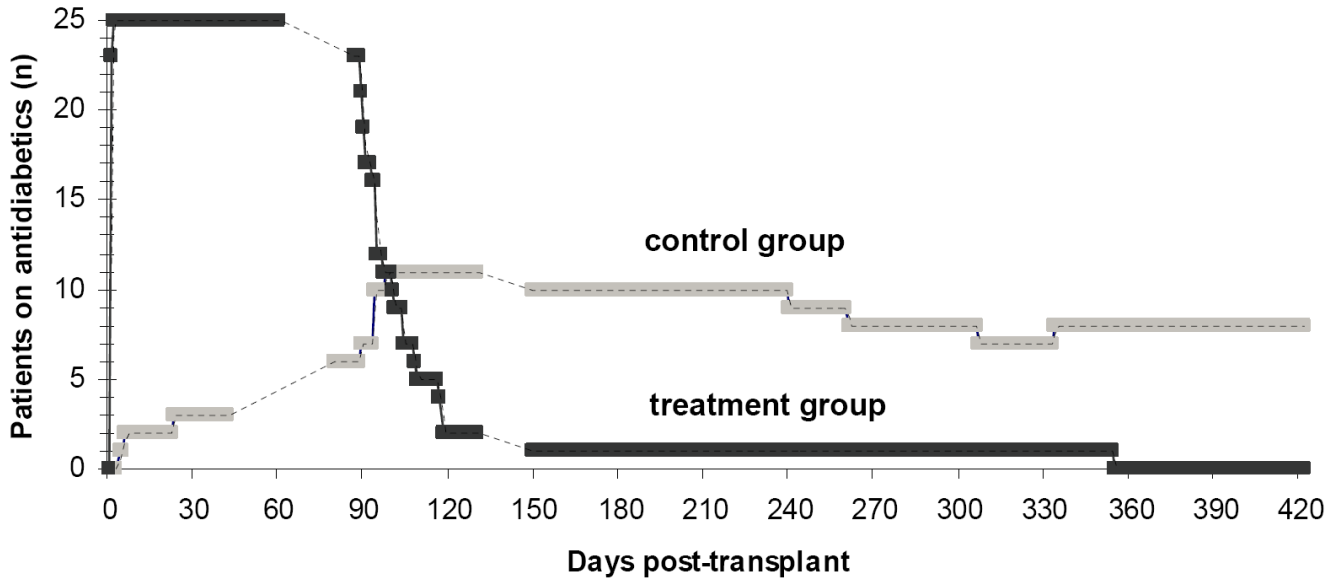
- Treatment starts when evening BG ≥140 mg/dl
- BG target level: 110-120 mg/dl
- Treatment with long acting insulin (Insulatard®)

Arm B (control):

- Corrections at the latest when BG > 250 mg/dl
- BG target level: none, but 250 mg/dl not accepted
- Conventional BG lowering therapy, according to decisions of the ward

Hecking et al. J Am Soc Nephrol 2012

Early insulin for post-operative hyperglycaemia prevents PTDM at 1-year

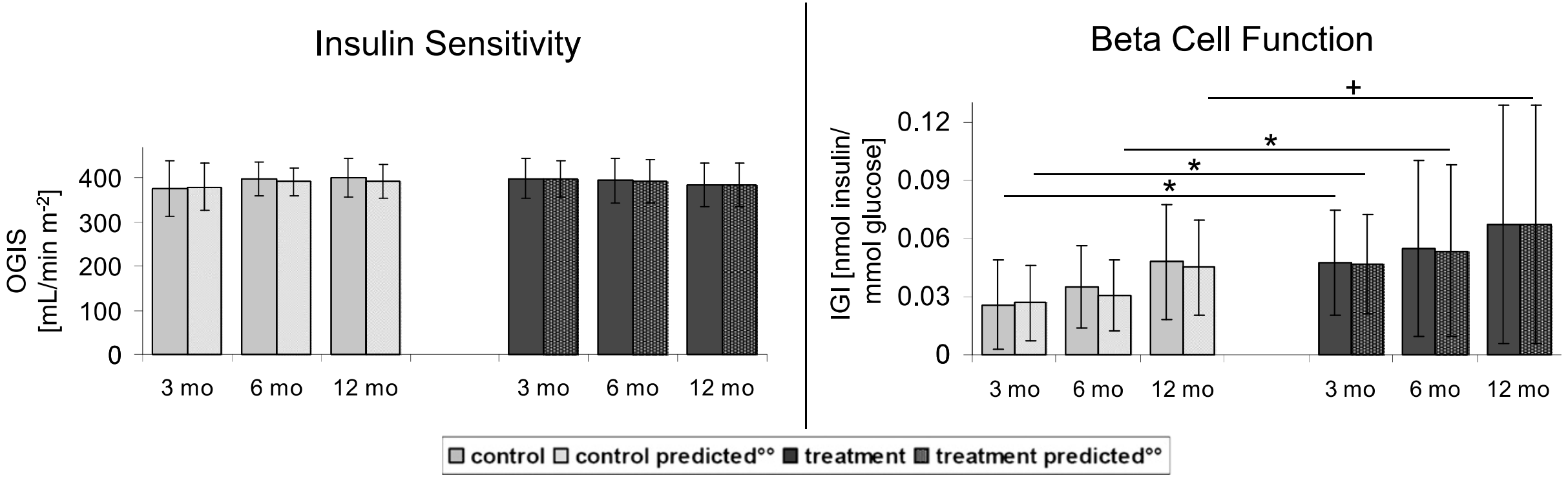


Odds Ratios [95% CI]

	Diabetic versus Non-diabetic	Diabetic + Prediabetic versus Normal
3 months	0.36 [0.11-1.16]	0.29 [0.08-1.09]
6 months	0.13 [0.03-0.53]	0.56 [0.16-1.92]
12 months	[illegible]	0.51 [0.16-1.61]
Overall^^	0.27 [0.10-0.72]	0.43 [0.16-1.14]

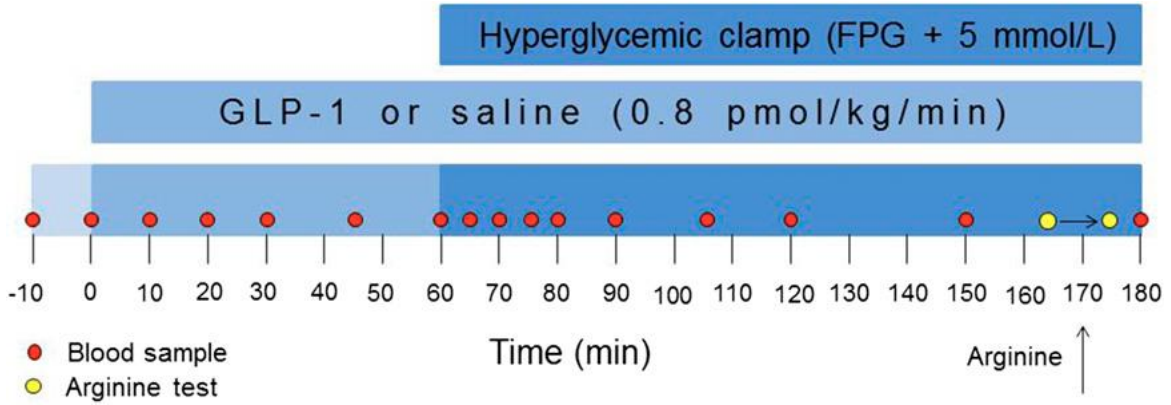
Hecking et al. J Am Soc Nephrol 2012

Benefit in treatment group due to improved beta-cell function (not insulin sensitivity)

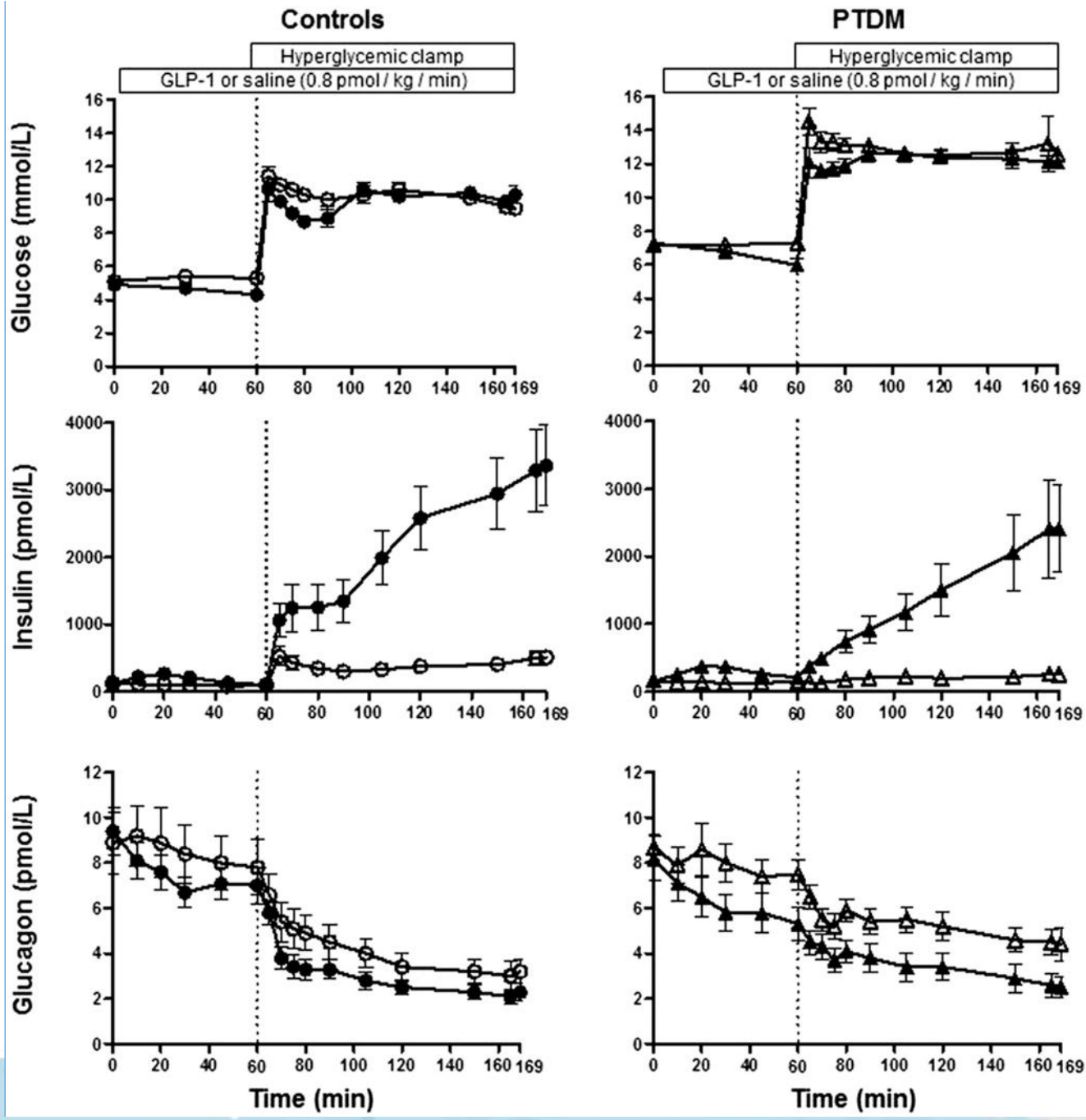


Hecking et al. J Am Soc Nephrol 2012

PTDM associated with reduced glucose-induced insulin secretion and attenuated glucagon suppression – restored by GLP-1



1) Pinelli et al. Diabetes Care 2013
2) Krisl et al. TTS 2014



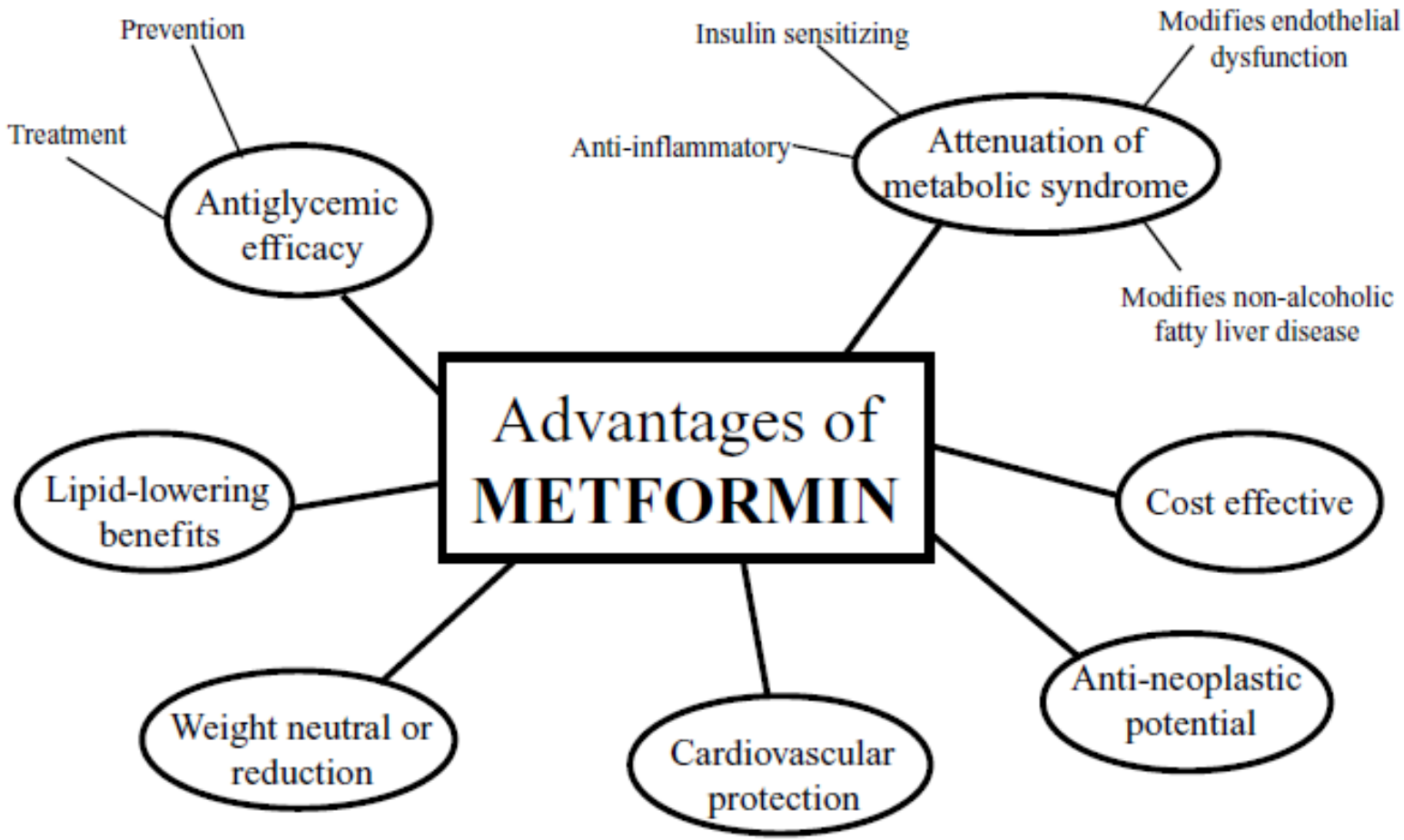
Halden et al. Diabetes Care 2016

SGLT-2 inhibitors for PTDM – can general population benefits translate to post-transplant cohort?

- Only one published case series of 6 SPK and 4 kidney-alone transplant recipients (variable exposure ~80 patient-months)
- Overall improvement seen in glycaemic control, weight, and blood pressure (similar magnitude effects as non-transplant cohorts)
- One patient experienced hypoglycaemia that did not require hospitalisation and one patient developed cellulitis.
- No urinary or mycotic infections diagnosed during treatment
- No patient experienced acute rejection or AKI
  - Small reduction seen in eGFR (-4.3 ml/min)
  - Effect attributed to renal afferent arteriole vasoconstriction due to increased sodium delivery at the macula densa and tubuloglomerular feedback

Rajasekeran et al. Diabetes Care 2017

Should metformin be our anti-glycaemic agent of choice for PTDM?



Sharif A. Am J Transplant 2011

Metformin and other antidiabetic agents in renal failure patients

Jean-Daniel Lalau[1,2], Paul Arnouts[3], Adnan Sharif[4] and Marc E. De Broe[5]

[1]Service d'Endocrinologie et de Nutrition, Centre Hospitalier Universitaire, Amiens, France; [2]Unité INSERM U-1088, Université de Picardie Jules Verne, Amiens, France; [3]Department of Nephrology-Diabetology-Endocrinology, AZ Turnhout, Turnhout, Belgium; [4]Department of Nephrology and Transplantation, Renal Institute of Birmingham, Queen Elizabeth Hospital, Birmingham, UK and [5]Laboratory of Pathophysiology, University of Antwerp, Wilrijk, Belgium

CONCLUSION

Metformin should itself be no longer considered a paradox. After more than half a century of experience, clinical studies continue to shed new light on the multiple beneficial effects of this drug. In addition, it will probably be clinically feasible in the near future to continue metformin therapy in cases of severe CKD.

Lalau et al. Kidney Int 2015

Open Access Protocol

BMJ Open

Protocol for a pilot randomised controlled trial of metformin in pre-diabetes after kidney transplantation: the Transplantation and Diabetes (Transdiab) study

Basil Alnasrallah,[1] Helen Pilmore,[1,2] Paul Manley[1]

Primary outcomes

Feasibility

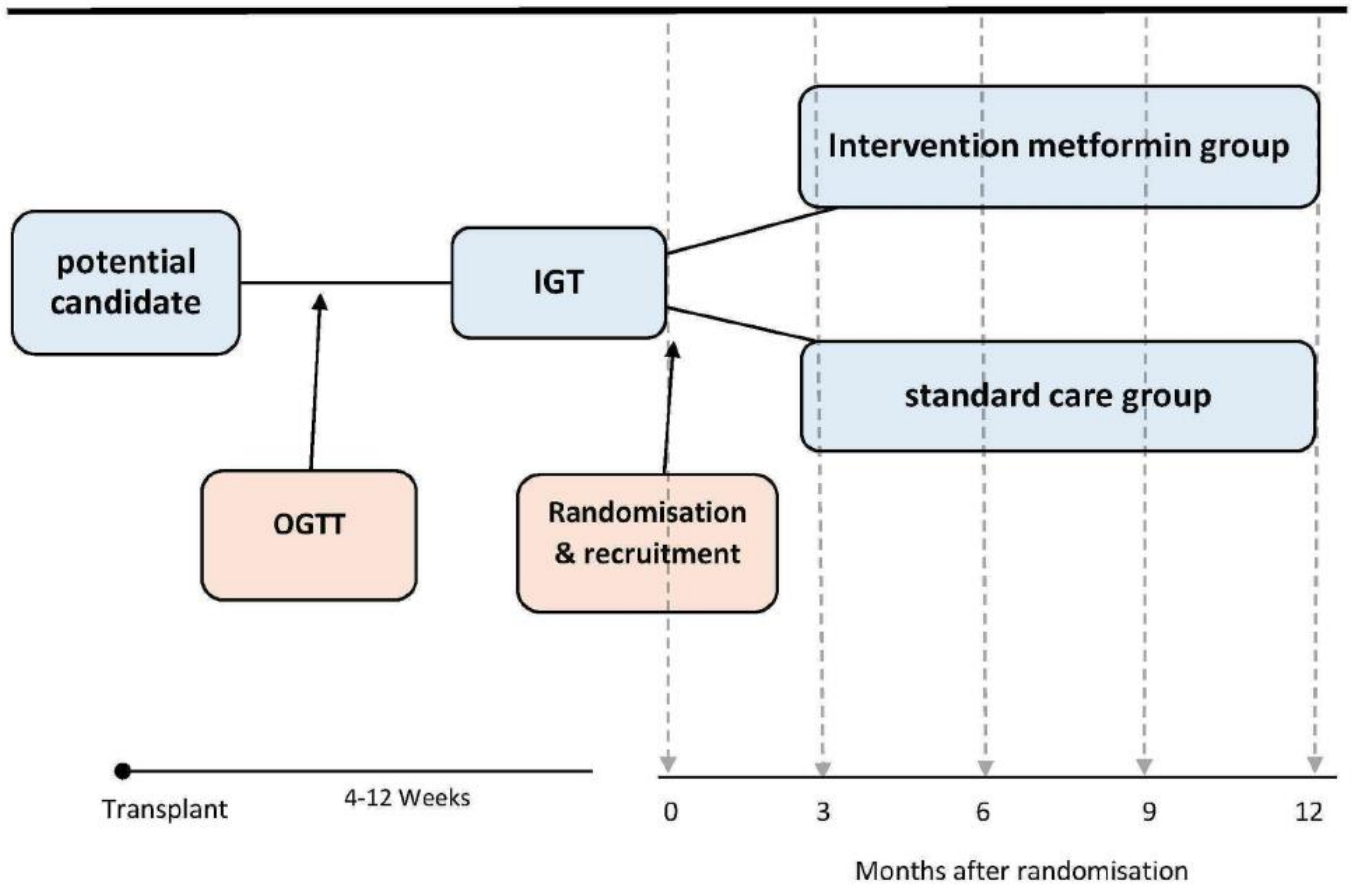
- Feasibility of recruitment will be assessed by the ratio of the number of randomised patients to the number of patients screened with OGTTs.

Tolerability

- Tolerability of metformin will be assessed using the GI Symptom Rating Scale (GSRS), a tool that has been validated to assess symptoms in gastrointestinal disorders such as gastro-oesophageal reflux disease and irritable bowel syndrome35 36 at baseline, 3 and 12 months postrandomisation.

Efficacy

- Efficacy of metformin will be assessed by HbA1c and morning glucose levels at baseline, 3, 6, 9 and 12 months post-randomisation.



Alnasrallah et al. BMJ Open 2017

Research in progress

Trials in progress

Study description	Number of patients	Status	Date last updated	Registration number
Effects of insulin or oral anti-diabetes mellitus drugs				
Early insulin therapy to prevent new-onset diabetes	251	Completed	March 2018	NCT01683331
	276	Completed recruitment	May 2018	NCT03507829
Sitagliptin to prevent new-onset diabetes in kidney patients	50	Recruiting	May 2018	NCT01928199
Sensor-augmented insulin-pump therapy in new-onset diabetes	85	Completed	June 2018	NCT01680185
Empagliflozin in renal transplant recipients (EMPA-RenalTx)	50	All recruited	June 2018	NCT03157414
Empagliflozin in PTDM	16	Recruiting	April 2017	NCT03113110
Studies focusing on the effects of glucocorticosteroids				
Different steroid withdrawal groups and new-onset diabetes	152	Recruiting	March 2014	NCT02095418
Budesonide for liver transplant immune suppression	40	Recruiting	October 2018	NCT03304626
Steroid avoidance and low-dose CNI and ATG-induction (SAILOR)	200	Recruiting	November 2016	NCT02083991
Steroid free immunosuppression and CNI minimization and PTDM	300	Recruiting hold	January 2015	NCT01560572
Studies focusing on other immunosuppression				
Pilot study comparing low-target and conventional-target Advagraf	30	Recruiting	June 2016	NCT01265537
DSA formation, diabetes and more, everolimus regimen (ADVISE)	90	All recruited	October 2018	NCT02316938
Everolimus and low-dose tacrolimus in renal recipients (PROTECT)	234	Unknown	September 2014	NCT02036554
NODAT in kidney transplant patients receiving belatacept	32	Unknown	2013	NCT01875224
Studies with vitamin D and magnesium supplementation				
Vitamin D supplementation in renal transplant recipients (VITALE)	320	All recruited	December 2017	NCT01431430
Magnesium supplement and insulin in renal transplant recipients	70	All recruited	January 2017	NCT01291030
Lifestyle intervention				
Active versus passive lifestyle on glycaemic benefits in renal transplant recipients (CAVIAR)	130	Recruiting	October 2017	NCT02233491

Jenssen & Hartmann. Nat Rev Endo 2019

Funded by EFSD, British Renal Society and Kidney Care UK

Glucometabolic effects comparing active lifestyle intervention using renal dietitian-led behaviour change techniques versus standard of care after kidney transplantation (CAVIAR): a randomised controlled trial

Kulli Kuningas[1], Joanne Driscoll[2], Reena Mair[2], Helen Smith[3], Mary Dutton[1], Edward Day[4], Adnan Sharif[1,5]

[1]Department of Nephrology and Transplantation, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK

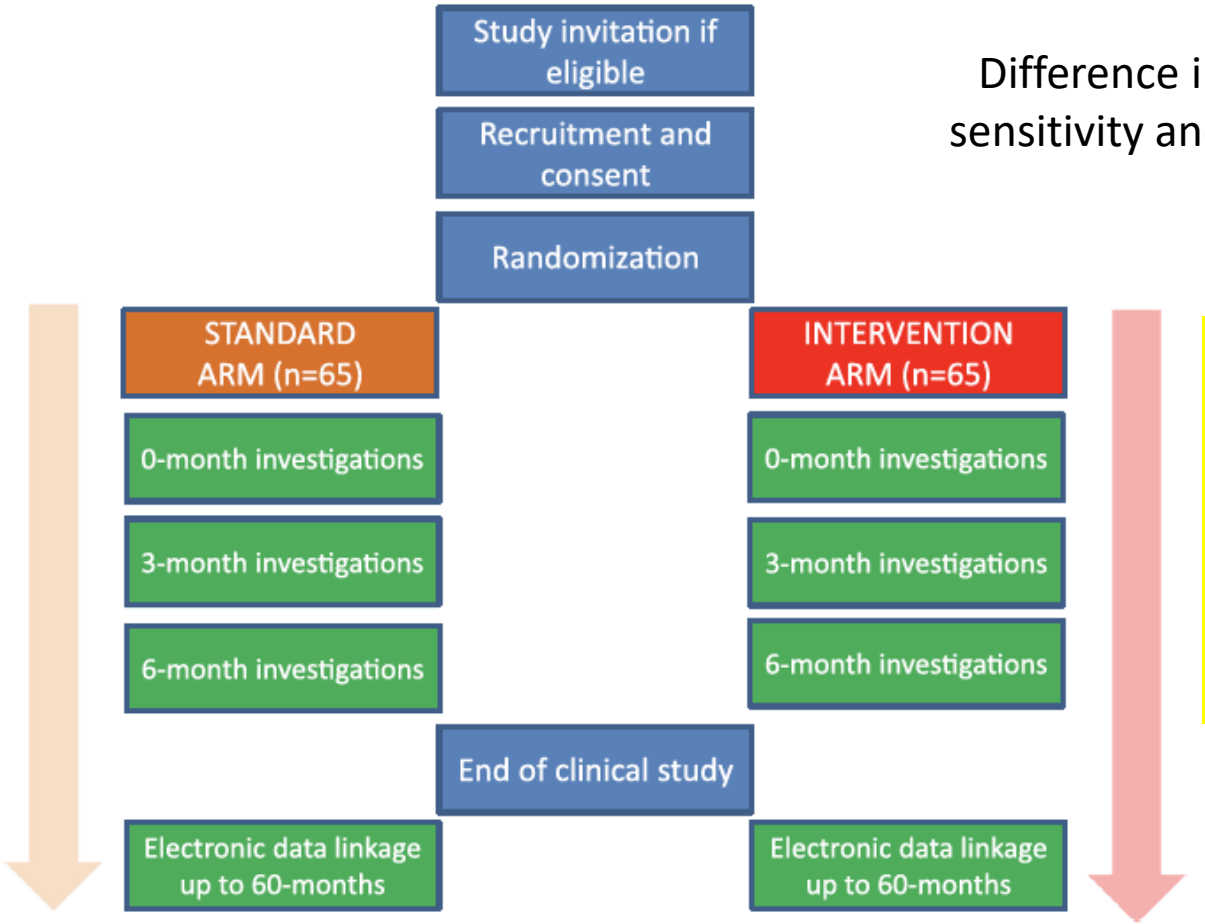
[2]Department of Nutrition and Dietetics, Queen Elizabeth Hospital, Birmingham, UK

[3]Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

[4]National Addiction Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[5]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK

CAVIAR trial design



Primary endpoint

Difference in insulin secretion, sensitivity and disposition index

Intervention by renal dietitian using evidence-based 'Behaviour Change Techniques'

Fig. 1 Trial design for the CAVIAR study showing randomisation arms comparing active versus passive lifestyle intervention in 130 nondiabetic kidney allograft recipients

Wilcox et al. Trials 2016

PARAMETER		ACTIVE	PASSIVE
Number		66	64
Age in years (± SD)		47·7 ± 13·3	47·4 ± 13·7
Male sex*		31 (43·7%)	40 (56·3%)
Ethnicity*	White	46 (69·7%)	42 (65·6%)
	Black	8 (12·1%)	6 (9·4%)
	South Asian	12 (18·2%)	13 (20·3%)
	Chinese	0 (0·0%)	1 (1·6%)
	Mixed race	0 (0·0%)	1 (1·6%)
	Other	0 (0·0%)	1 (1·6%)
Cytomegalovirus serostatus positive		26 (39·4%)	27 (42·2%)
Hepatitis C positive		0 (0·0%)	0 (0·0%)
Family history of diabetes		20 (37·0%)	18 (36·7%)
Repeat kidney transplant		7 (12·5%)	6 (12·2%)
Post-transplant time in days (±SD)		269 ± 181	249 ± 150
Immunosuppression	Tacrolimus	66 (100·0%)	64 (100·0%)
	Mycophenolate Mofetil	57 (86·4%)	57 (89·0%)
	Mycophenolic Acid	7 (10·6%)	5 (7·8%)
	Azathioprine	2 (3·0%)	2 (3·2%)
	Prednisolone	66 (100·0%)	64 (100·0%)
Body mass index* (kg/m^2) (± SD)		27·8 ± 4.4	27·7 ± 4.4
Glycaemic status	Normal	36 (54·5%)	38 (59·4%)
	Pre-diabetes	21 (31·8%)	19 (29·7%)
	PTDM	9 (13·6%)	7 (10·9%)

CAVIAR study outcomes

Primary endpoint

- Insulin secretion (mean difference -446 [-3184 to 2292], p=0.748)
- Insulin sensitivity (mean difference -0.45 [-1.34 to 0.44], p=0.319)
- Disposition index (mean difference -940 [-5655 to 3775], p=0.693)

Selected secondary endpoints

- Weight difference (mean difference -2.47kg [-.401 to -0.92], p=0.002)
- Free fat mass (mean difference -1.54kg [-3.24 to 0.16], p=0.075)
- Post-transplantation diabetes (7.6% versus 15.6% respectively, p=0.123)

RANDOMISATION GROUP	GLYCAEMIC STATUS AT BASELINE	GLYCAEMIC STATUS AT FOLLOW UP			P VALUE
		Normal	Pre-diabetes	PTDM	
Active intervention	Normal				
	Pre-diabetes				
	PTDM				
Passive intervention	Normal				
	Pre-diabetes				
	PTDM				
Total	Normal				
	Pre-diabetes				
	PTDM				

Interpretation of negative study: why did primary outcome fail?

- Is the intervention ineffective???
- Validation work for surrogates of glucose metabolism after kidney transplantation were derived exclusively from recipients of white ethnicity
  - 33.8% of participants in CAVIAR were from the BAME community
- Disposition index is conceptually useful but may not true reflection of dynamic glucose metabolism
  - The hyperbolic relationship between insulin secretion and sensitivity has recently been shown to be different between ethnic groups
  - The disposition index is paradoxically higher among non-whites due to greater compensatory increase of insulin secretion to insulin sensitivity
  - Ignores liver influence on insulin sensitivity
- Glucose metabolism post kidney transplantation is too volatile
- There is a significant level of dysglycaemia among prevalent kidney transplant recipients (surrogate measures of glucose metabolism may therefore be irrelevant in this setting and never been validated in this setting)

Summary/Conclusions

Summary/Conclusions

- PTDM is a common medical complication after kidney transplantation with associated adverse outcomes for kidney allograft recipients
- Our clinical approach to PTDM is limited by a lack of firm evidence and cannot simply mirror our approach with the general population
- Management of PTDM requires a combined approach from transplant clinicians and diabetologists:
  - Choosing the appropriate anti-glycaemic agent in the polypharmacy and complicated milieu of transplantation must be individualised for every patient
- Further research should help facilitate more pro-active interventions to prevent and/or manage PTDM

Further reading

American Journal of Transplantation 2014; 14: 1992–2000
Wiley Periodicals Inc.

doi: 10.1111/ajt.12

Meeting Report

Proceedings From an International Consensus Meeting on Posttransplantation Diabetes Mellitus: Recommendations and Future Directions

A. Sharif[1,*], M. Hecking[2], A. P. J. de Vries[3], E. Porrini[4], M. Hornum[5], S. Rasoul-Rockenschaub[2], G. Berlakovich[2], M. Krebs[2], A. Kautzky-Willer[2], G. Schernthaner[2], P. Marchetti[6], G. Pacini[7], A. Ojo[8], S. Takahara[9], J. L. Larsen[10], K. Budde[11], K. Eller[12], J. Pascual[13], A. Jardine[14], S. J. L. Bakker[15], T. G. Valderhaug[16], T. G. Jenssen[17], S. Cohney[18] and M. D. Säemann[2]

Lancet Diab Endo 2016

Review

Post-transplantation diabetes—state of the art

Adnan Sharif, Solomon Cohney

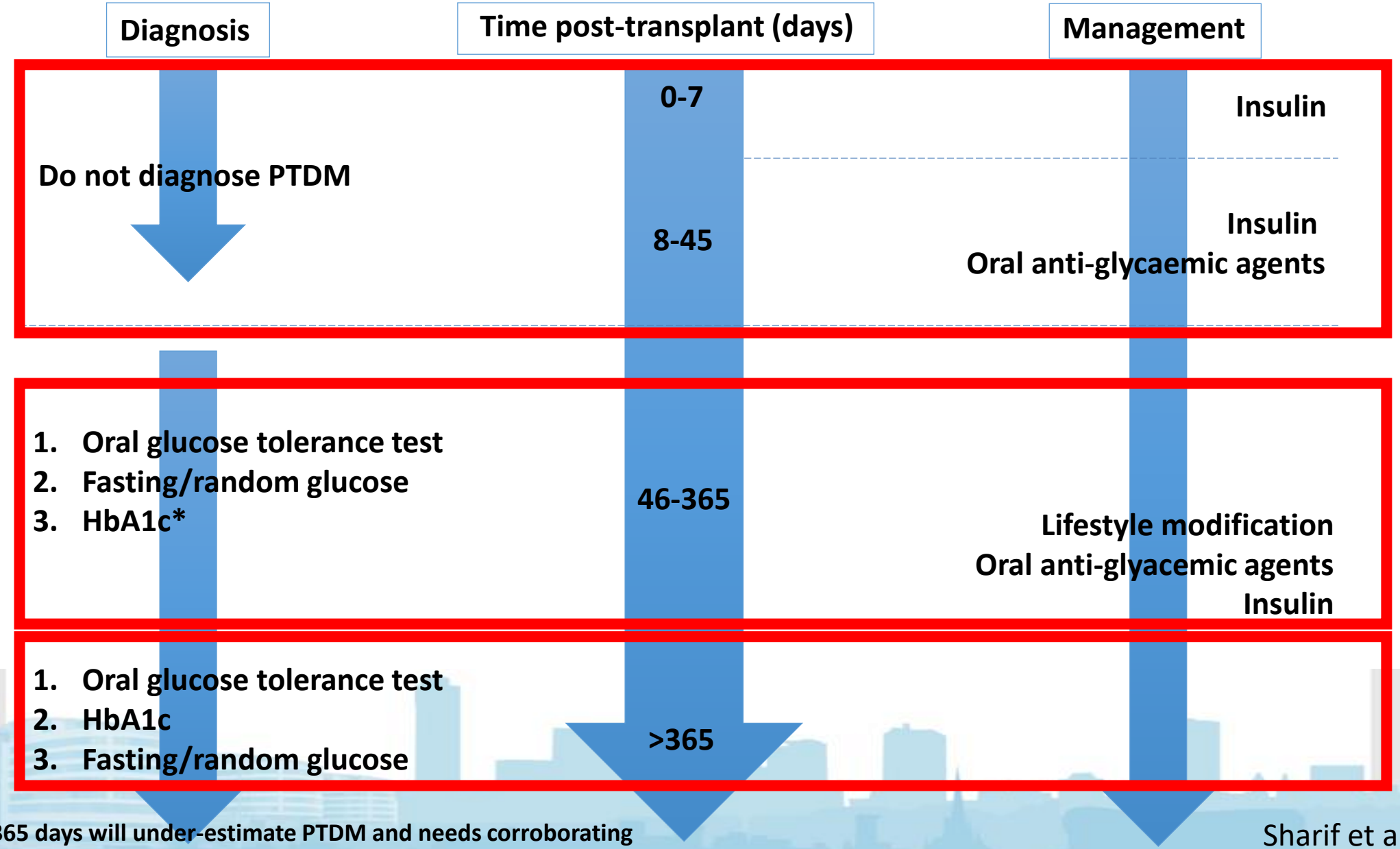
Nat Rev Endo 2019

REVIEWS

Post-transplant diabetes mellitus in patients with solid organ transplants

Trond Jenssen[1,2] and Anders Hartmann[1,2]*

Diagnosis and management of PTDM: International Consensus guidelines



* HbA1c alone <365 days will under-estimate PTDM and needs corroborating

Sharif et al. AJT 2014

Thank you for you attention

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