Management of diabetics with advanced CKD

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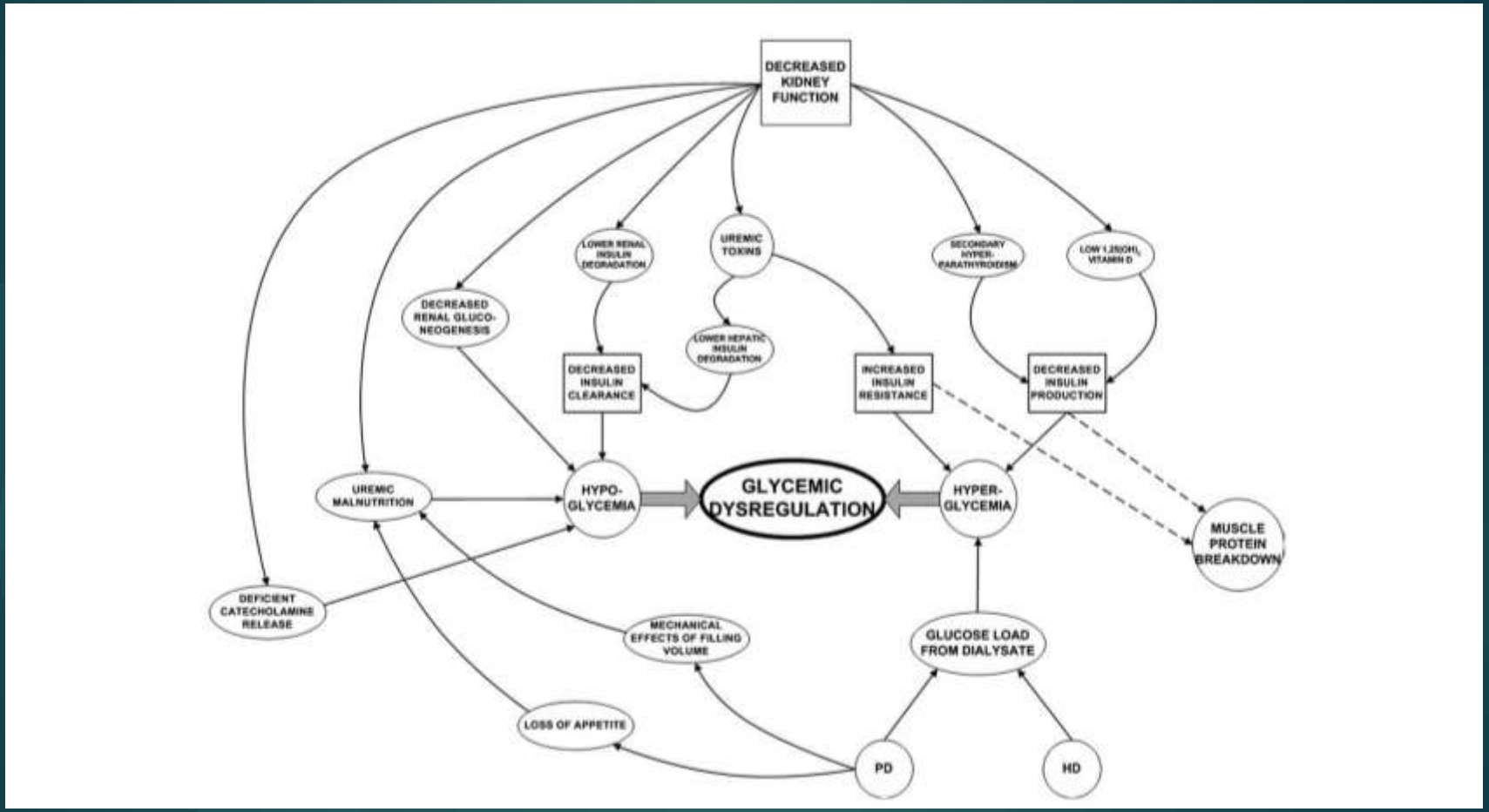
Antidiabetic Drugs

V·T·E	Oral anti-diabetic drugs and Insulin analogs (A10)			
Insulin	Sensitizers	Biguanides		Metformin[#] · Buformin[‡] · Phenformin[‡]
		TZDs/"glitazones" (PPAR)		Pioglitazone · Rivoglitazone[†] · Rosiglitazone · Troglitazone[‡]
		Dual PPAR agonists		Aleglitazar[†] · Muraglitazar[§] · Saroglitazar · Tesaglitazar[§]
	Secretagogues	K+ ATP	Sulfonylureas	*1st generation*: Acetohexamide · Carbutamide · Chlorpropamide · Metahexamide · Tolbutamide · Tolazamide *2nd generation*: Glibenclamide (Glyburide)[#] Glibornuride · Glipizide · Gliquidone · Glisoxepide · Glyclopyramide · Glimepiride · Gliclazide
			Meglitinides/"glinides"	Nateglinide · Repaglinide · Mitiglinide
		GLP-1 agonists		Exenatide · Liraglutide · Taspoglutide[†] · Albiglutide[†] · Lixisenatide · Dulaglutide[†] · Semaglutide
		DPP-4 inhibitors		Alogliptin · Anagliptin · Gemigliptin · Linagliptin · Saxagliptin · Sitagliptin · Teneligliptin · Vildagliptin
		GPR40 Free fatty acid receptor 1		Fasiglifam[†]
	Analogs/other insulins			*fast-acting* (Insulin lispro · Insulin aspart · Insulin glulisine) · *short-acting* (Regular insulin) · *long-acting* (Insulin glargine · Insulin detemir · NPH insulin) · *ultra-long-acting* (Insulin degludec[†]) · *inhalable* Exubera[‡]
Other	Alpha-glucosidase inhibitors			Acarbose · Miglitol · Voglibose
	Amylin analog			Pramlintide
	SGLT2 inhibitors			Canagliflozin · Dapagliflozin · Empagliflozin[†] · Remogliflozin[§] · Sergliflozin[§] · Tofogliflozin[†]
	Other			Bromocriptine · Benfluorex[‡] · Tolrestat[‡]

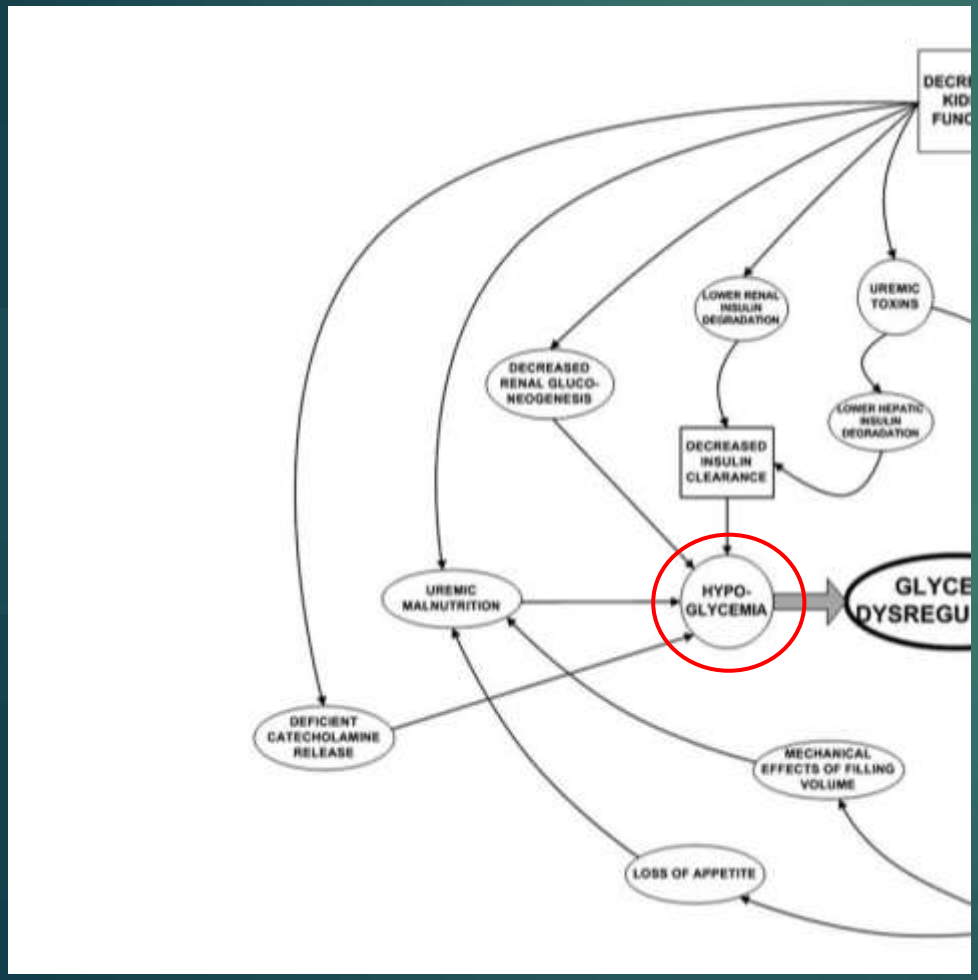
[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([†]Phase III · [§]Never to phase III)

CKD and Glycaemic Control



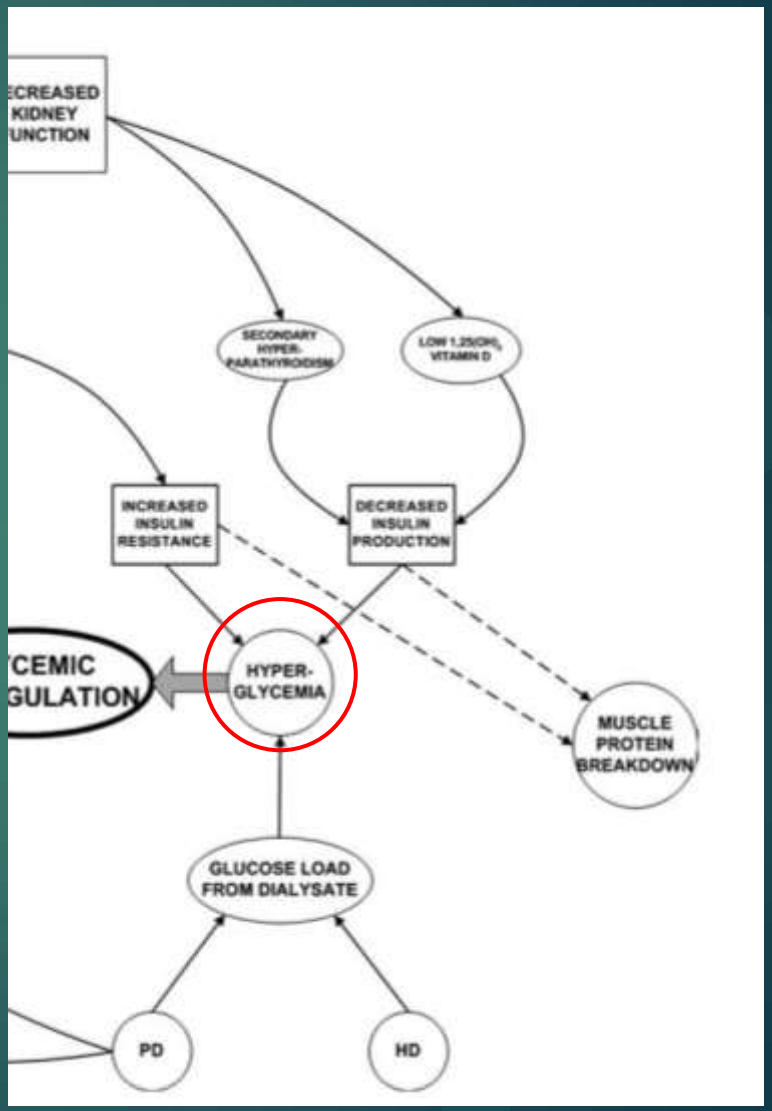
Kovesdy AJKD 52:766 2008

CKD and Glycaemic Control



Kovesdy AJKD 52:766 2008

CKD and Glycaemic Control



Kovesdy AJKD 52:766 2008

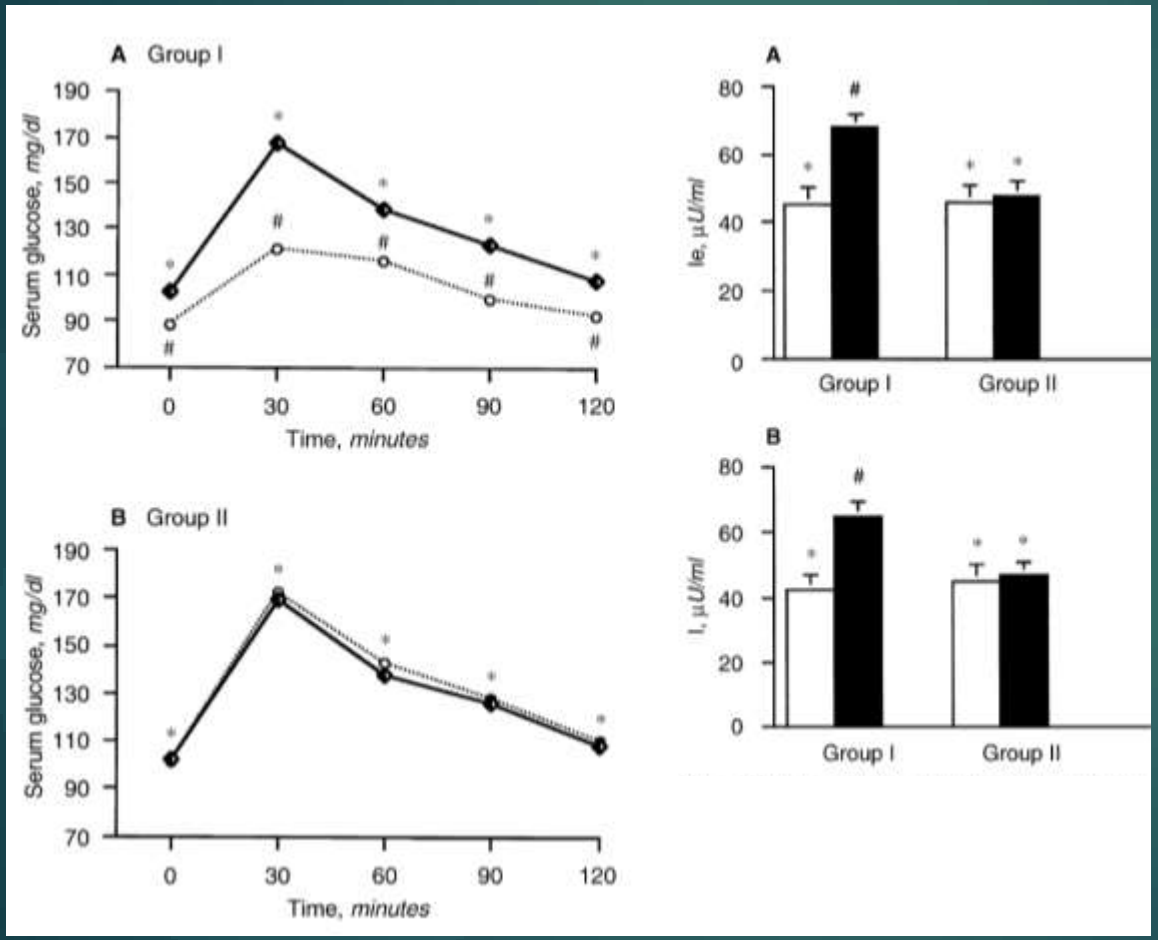
Vit D & T2DM: Trials

Author	Trial	Pts.	Rx	Time (wks)	No. (A/C)	Results
Gedik 86	C	NonDM	Vit D 50 µg/d	26	4/10	IS↑ II↑
Inomata 86	C	DM	1α 2 µg/d	3	7/7	IS↑
Boucher 95	NC	DM	Vit D 2,500 µg once i.m.	10	22/0	IS↑
Borissova	C	DM	Vit D 35µg/d	4	10/17	IS↑
Von Hurst 10	RCT	IR	Vit D 100µg/d	26	42/39	IS↑ IR↓
Sabherwal 10	NC	DM	Target [25-OHD] >50 nM		52/0	HbA1c↓ -0.7%
Nikoyeh 11	RCT	DM	Vit D 12.5 µg/d	12	60/30	IR↓ IS↑
Mitri	RCT	IR	Vit D 50 µg/d	16	46/45	IS↑ DI↑
Eftekari	RCT	DM	1α 0.5 µg/d	12	35/35	IS↑

C: controlled.
IR: Insulin resistance.
II: insulinogenic index

NC: no control. RCT: randomized controlled trial
IS: Insulin sensitivity DI: Disposal index

1,25-Vitamin D improves Insulin Sensitivity



Oral glucose tolerance test
Before: ◊ and after: o

16 Insulin resistant
HD patients

PTH 798 pg/ml
did not change during study

RCT
1.8 µg 1,25-vitamin D
X3/week for 4 weeks
vs. Control (group 2)

Triglycerides 198→148 mg/dL

Euglycaemic clamp study
A: Insulin stimulated
glucose metabolism
B: Insulin concentration

Mak KI 53,1353 1998

Parathyroidectomy improves insulin secretion in uraemic dogs

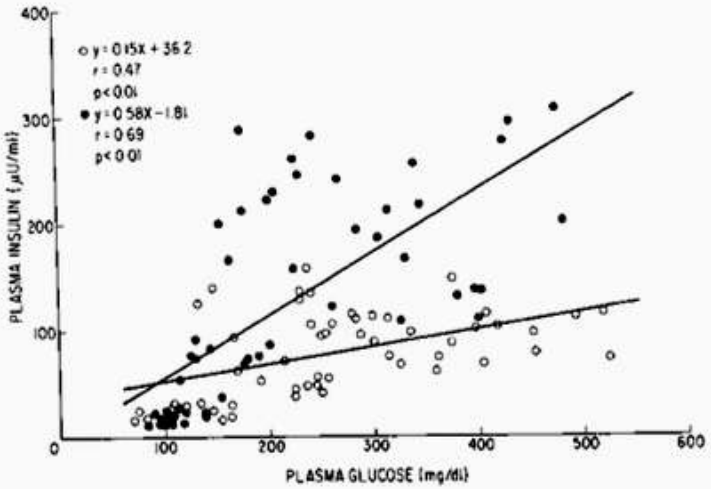


Figure 5. The relationship between plasma insulin and glucose concentrations observed during intravenous glucose tolerance tests performed in NPX (○) and NPX-PTX (●).

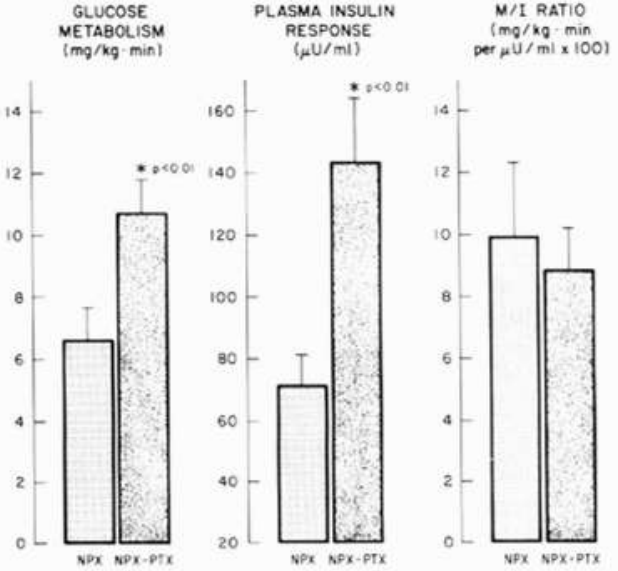
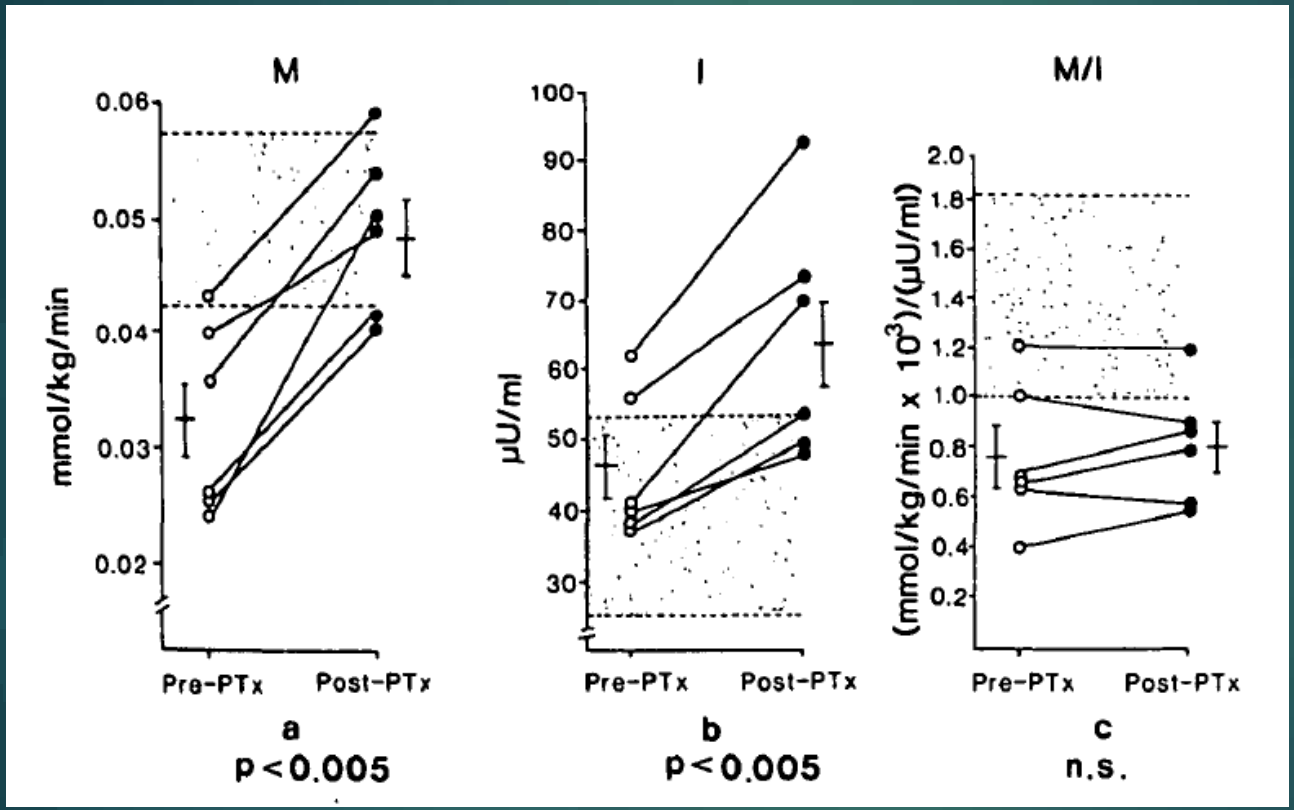


Figure 6. Glucose metabolism, total insulin response, and M/I ratio observed during the hyperglycemic clamp in NPX and NPX-PTX dogs. Each column represents the mean of data from six NPX and seven NPX-PTX dogs. The brackets denote 1 SE. Star indicates significant difference from NPX with $P < 0.01$.

Akmal J Clin Invest 75:1037 1985

Parathyroidectomy improves Insulin Secretion in HD



6 insulin-resistant HD pts.

Hyperglycaemic clamp study

PTH 3500 →210 ng/l

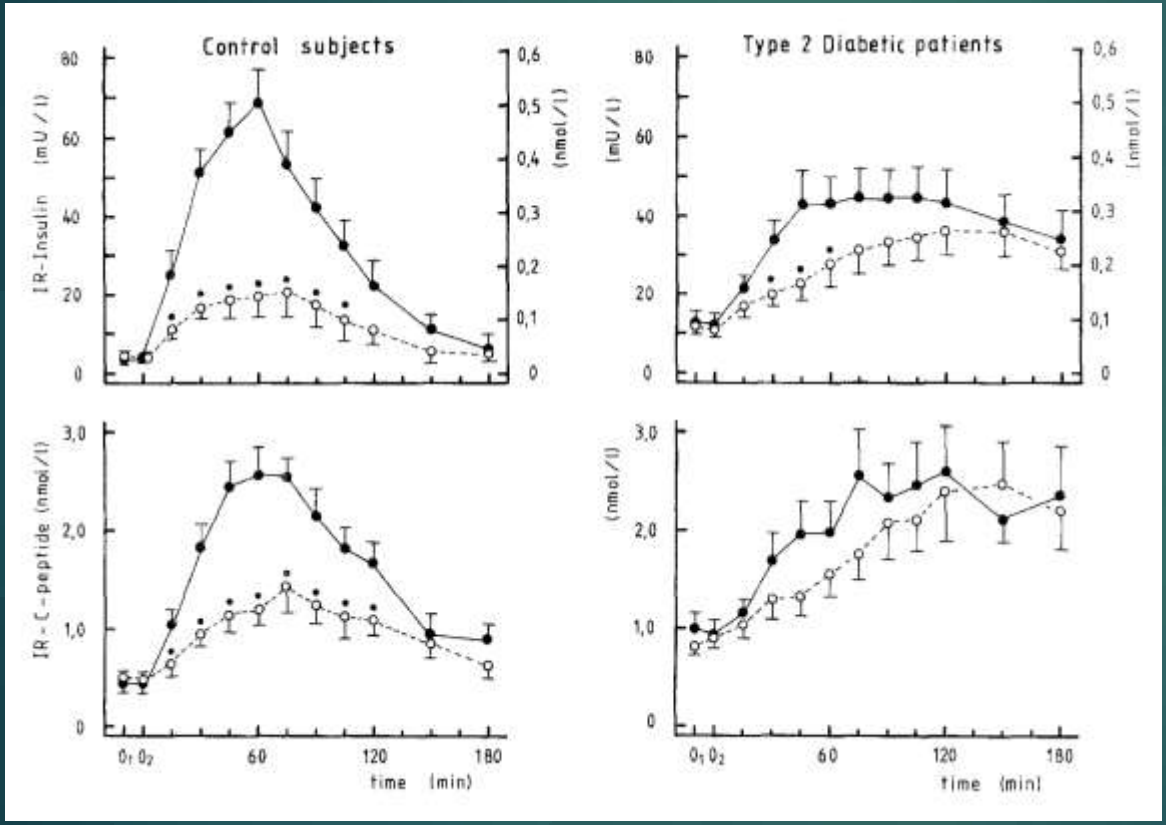
Glucose Metabolic Rate

Insulin levels (β-cell response to glucose↑)

Tissue sensitivity to insulin

Mak J Clin Endocrin Metab 60:229 1985

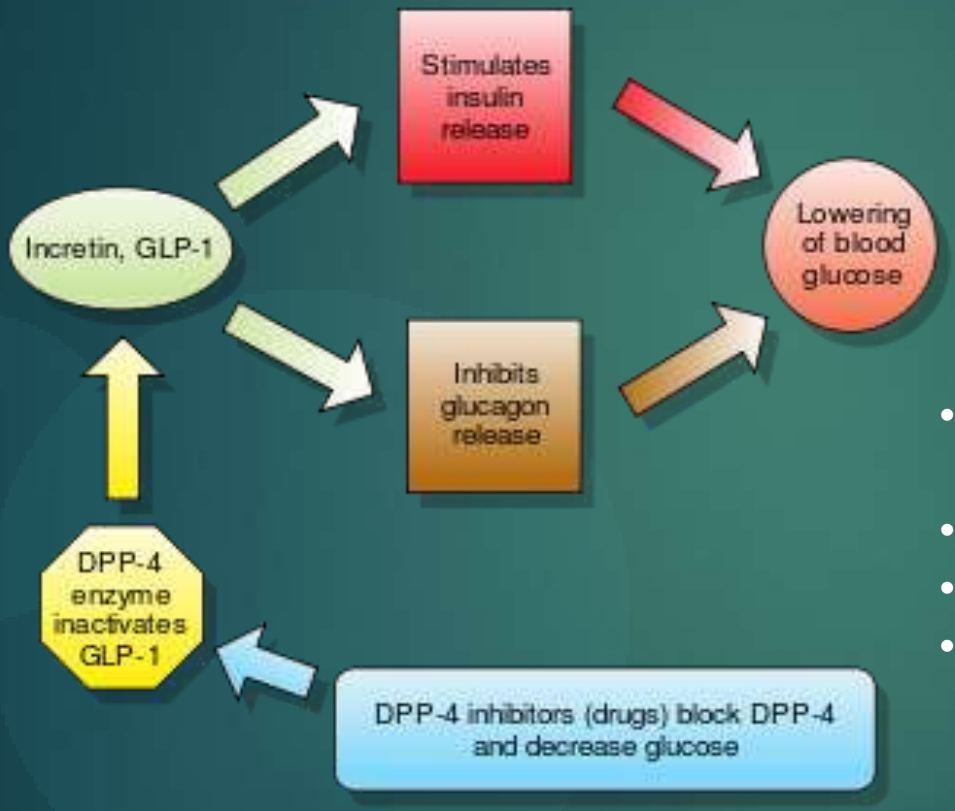
The Incretin Effect



●: Oral glucose load
O: Isoglycaemic IV glucose infusion

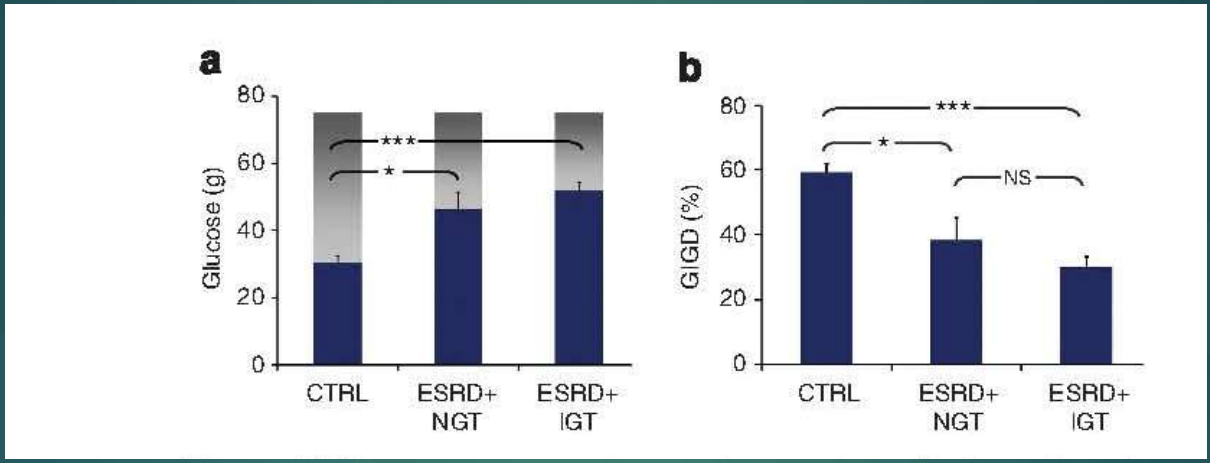
Nauck Diabetologia 29,46 1986

Incretins

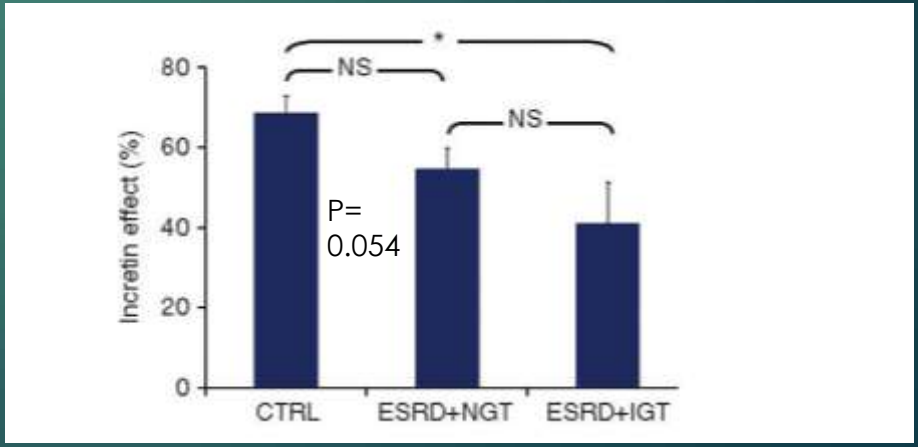


- Gastric inhibitory peptide (GIP) & Glucagon-like peptide (GLP-1)
- Secreted by intestinal mucosa
- Increases insulin secretion
- Inhibits glucagon release

G-I mediated Glucose Disposal (GIDP) and Incretin Effect



Incretin effect = 100 x $\frac{AUC_{OGTT} - AUC_{IIGI}}{AUC_{OGTT}}$



Idorn KI 2013; 83:915

GLP-1 and GIP

Normal | ESRD Normal OGT | ESRD Impaired OGT

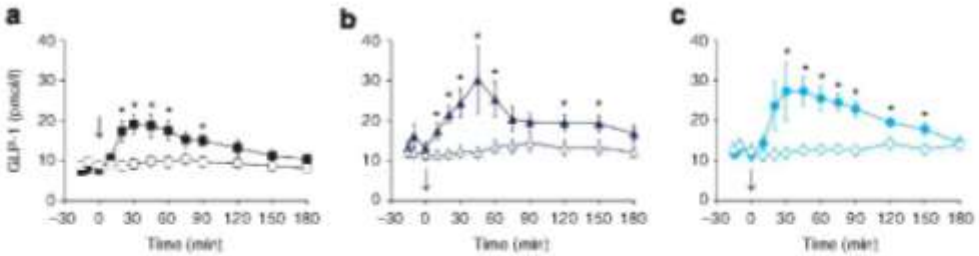


Figure 4 | Total glucagon-like peptide-1 (GLP-1). Plasma total GLP-1 responses during oral glucose tolerance test (filled symbols) and isoglycemic intravenous glucose infusion (open symbols) in healthy control subjects (**a**) and in patients with end-stage renal disease and normal glucose tolerance (**b**) or impaired glucose tolerance (**c**). Data are mean ± s.e.m. Asterisks (*) indicate significant ($P<0.05$) differences at individual time points and arrows (↓) indicate time of initiation of oral glucose ingestion.

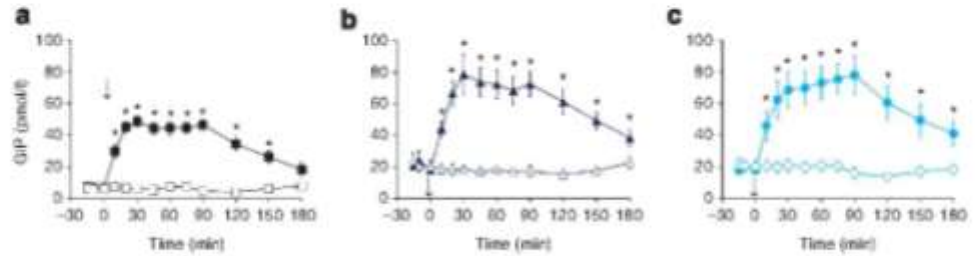


Figure 5 | Total glucose-dependent insulinotropic polypeptide (GIP). Plasma total GIP responses during oral glucose tolerance test (filled symbols) and isoglycemic intravenous glucose infusion (open symbols) in healthy control subjects (**a**) and in patients with end-stage renal disease and normal glucose tolerance (**b**) or impaired glucose tolerance (**c**). Data are mean ± s.e.m. Asterisks (*) indicate significant ($P<0.05$) differences at individual time points, and arrows (↓) indicate time of initiation of oral glucose ingestion.

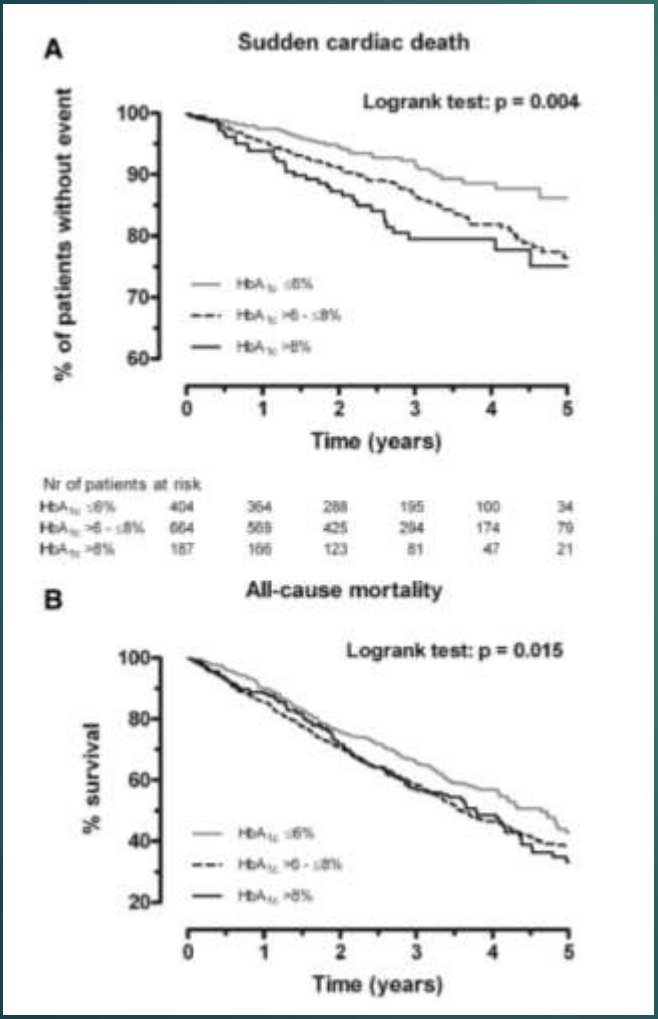
Basal GLP-1 and GIP higher in both ESRD groups ($p<0.01$)

Idorn KI 2013; 83:915

Glucose Metabolism & ESRD

- Reduced Incretin Effect
- Normal Incretin Production
- Ergo, Reduced β-cell reponse to incretin
- Elevated glucagon, cannot be suppressed by glucose
- Peripheral insulin resistance
- Fasting hyperinsulinaemia

Glycaemic Control & T2DM HD Survival: The 4D Study



- 1255 prevalent T2DM HD patients
- (RCT Simvastatin vs. Placebo)
- Baseline HbA1C

Adjusted Hazard Ratios per 1% increase in HbA1C

Sudden Death	1.21*
AMI	0.94
Stroke	1.11
CV Death	1.09*
Death	1.09*
Heart Failure Death	1.30*
Other Death	1.04

Drechsler Circulation 120:2421 2009

Hgb A1C & HD Mortality

DaVita Database

96% T2DM

Baseline

Average

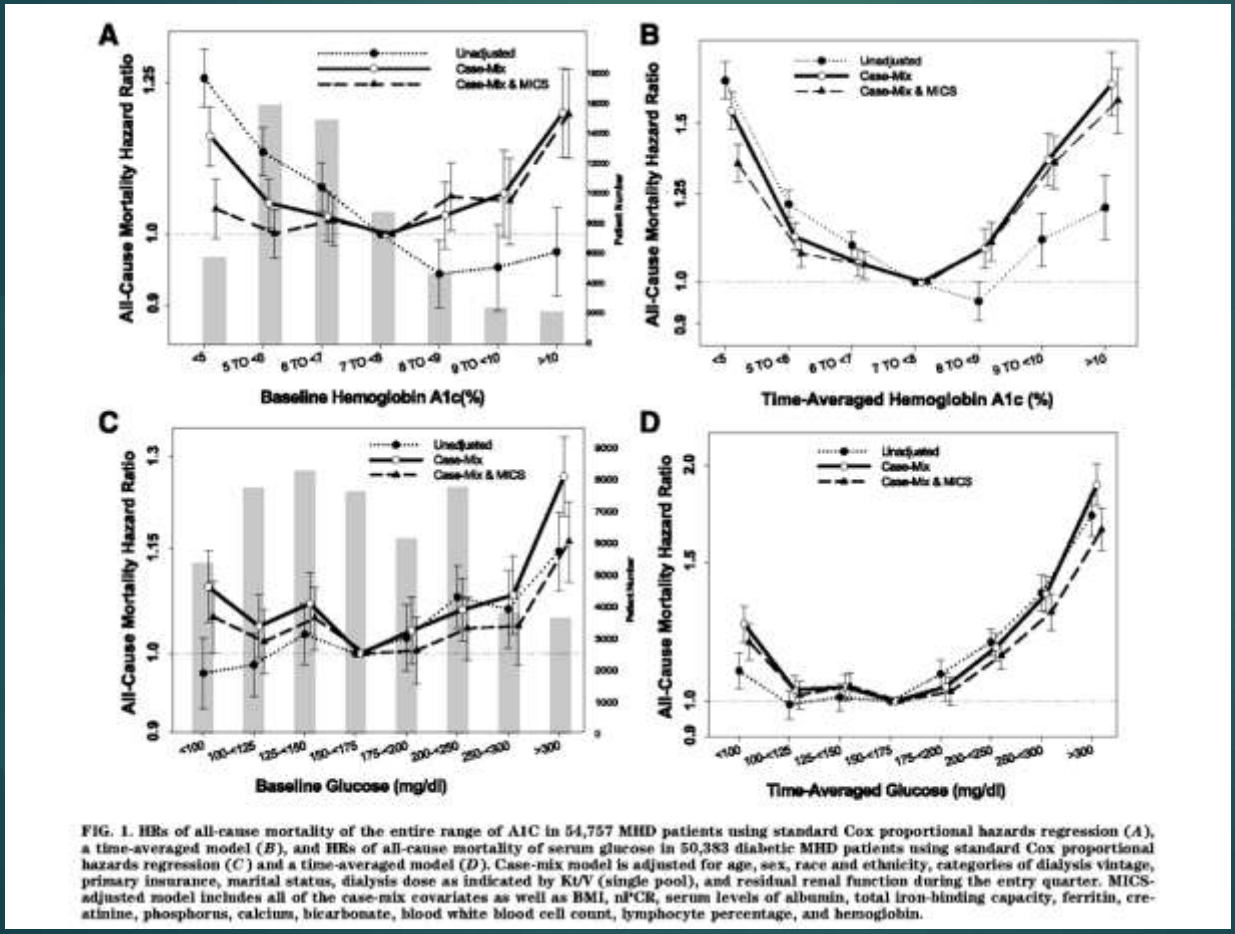


FIG. 1. HRs of all-cause mortality of the entire range of A1C in 54,757 MHD patients using standard Cox proportional hazards regression (*A*), a time-averaged model (*B*), and HRs of all-cause mortality of serum glucose in 50,383 diabetic MHD patients using standard Cox proportional hazards regression (*C*) and a time-averaged model (*D*). Case-mix model is adjusted for age, sex, race and ethnicity, categories of dialysis vintage, primary insurance, marital status, dialysis dose as indicated by Kt/V (single pool), and residual renal function during the entry quarter. MICS-adjusted model includes all of the case-mix covariates as well as BMI, nPCR, serum levels of albumin, total iron-binding capacity, ferritin, creatinine, phosphorus, calcium, bicarbonate, blood white blood cell count, lymphocyte percentage, and hemoglobin.

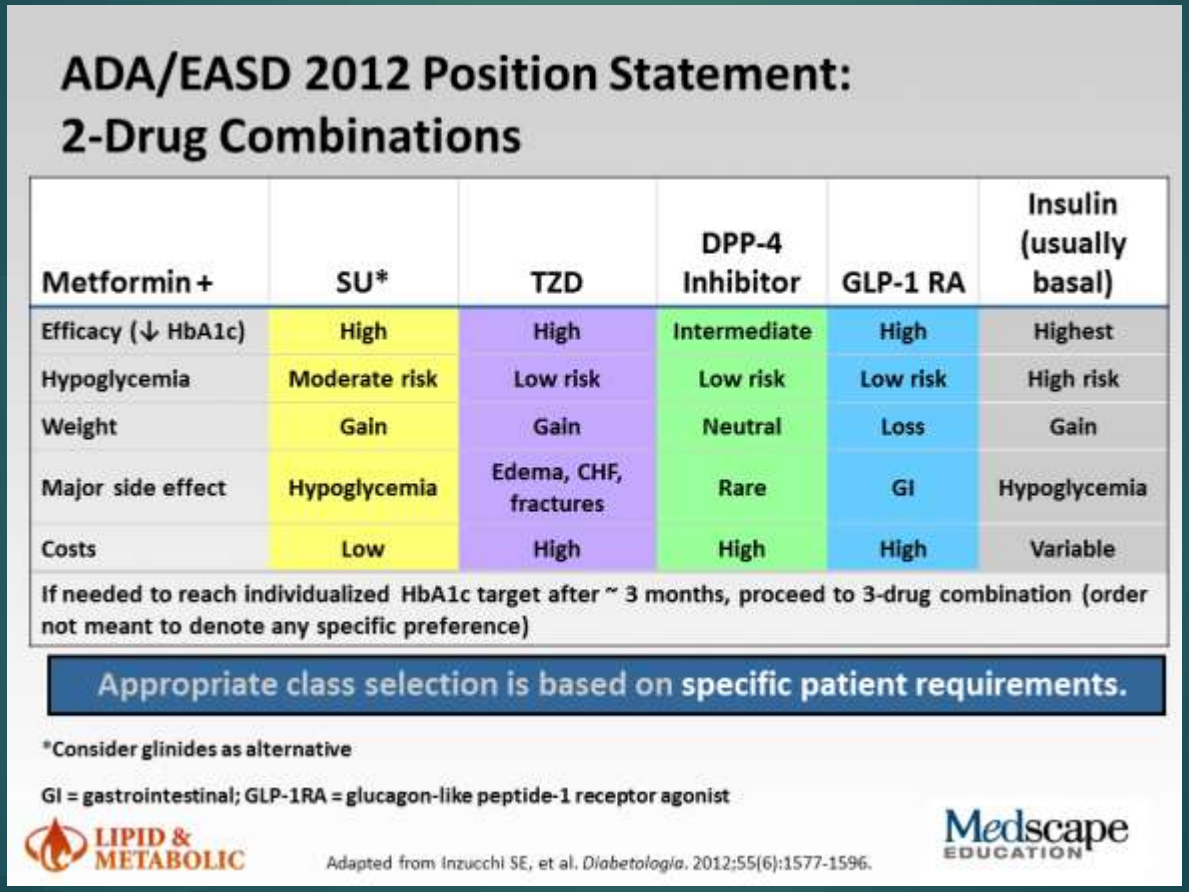
Hgb A1C

Random blood Glucose

(100 mg% = 5.5 mM)

Ricks Diabetes 2012; 61:708

American Diabetes Association – European Association for the Study of Diabetes (ADA/EASD) Guidelines



ADA/EASD 2012 Position Statement: 2-Drug Combinations

Metformin +	SU*	TZD	DPP-4 Inhibitor	GLP-1 RA	Insulin (usually basal)
Efficacy (↓ HbA1c)	High	High	Intermediate	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain
Major side effect	Hypoglycemia	Edema, CHF, fractures	Rare	GI	Hypoglycemia
Costs	Low	High	High	High	Variable

If needed to reach individualized HbA1c target after ~ 3 months, proceed to 3-drug combination (order not meant to denote any specific preference)

Appropriate class selection is based on **specific patient requirements.**

*Consider glinides as alternative

GI = gastrointestinal; GLP-1RA = glucagon-like peptide-1 receptor agonist

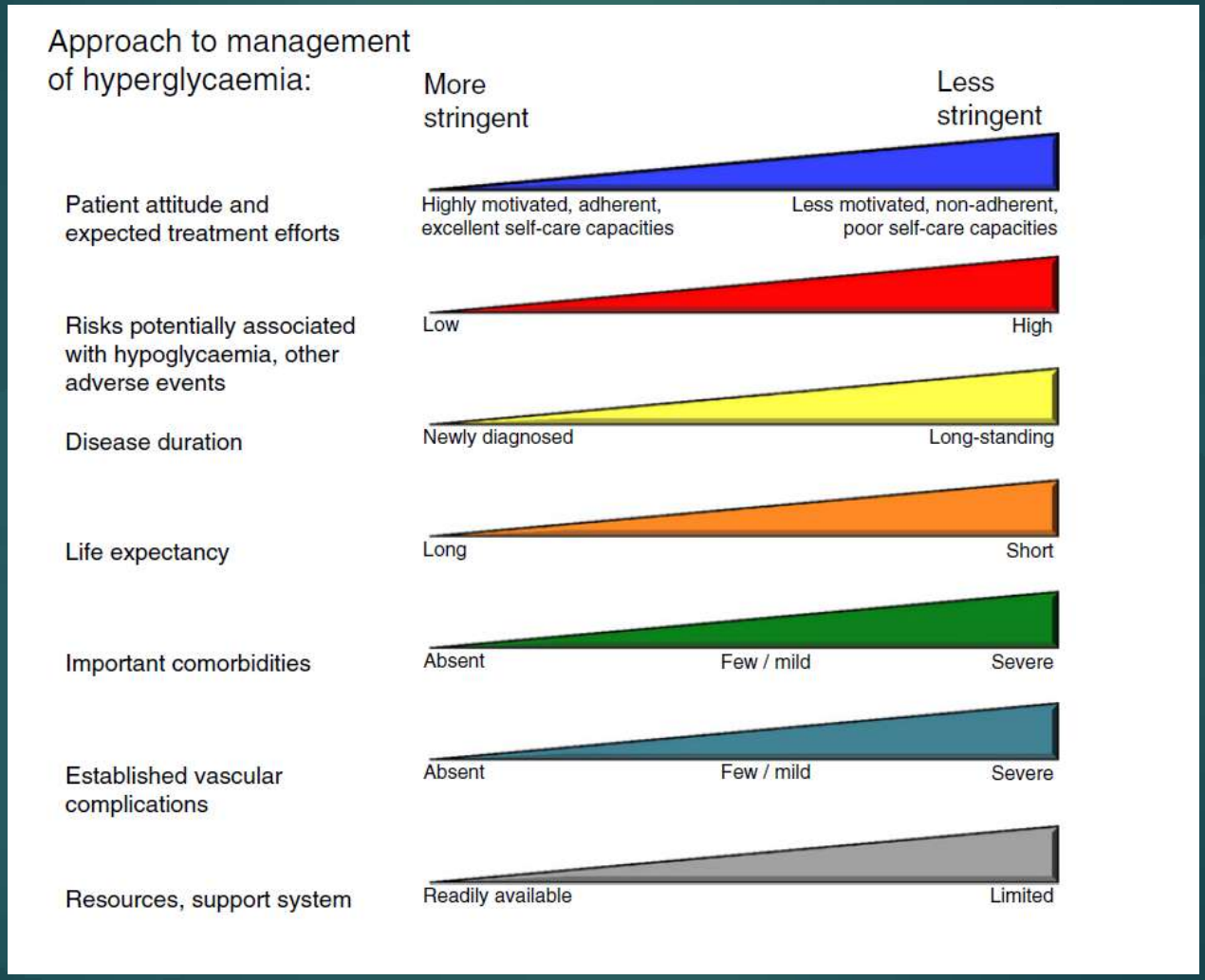
LIPID & METABOLIC

Adapted from Inzucchi SE, et al. *Diabetologia*. 2012;55(6):1577-1596.

Medscape EDUCATION

Inzucchi Diabetologia 55,1577 2012

Treatment should be individualised



Inzucchi Diabetologia 55,1577 2012

Chapter 2.1:

A: In patients with renal failure (eGFR <45 mL/min/1.73m²) or on dialysis, and diabetes mellitus should we intentionally aim to lower HbA1C by more tight glycaemic control

B: Is an aggressive treatment strategy (in number of injections and controls and follow up) superior to a more relaxed treatment strategy in patients using insulin?

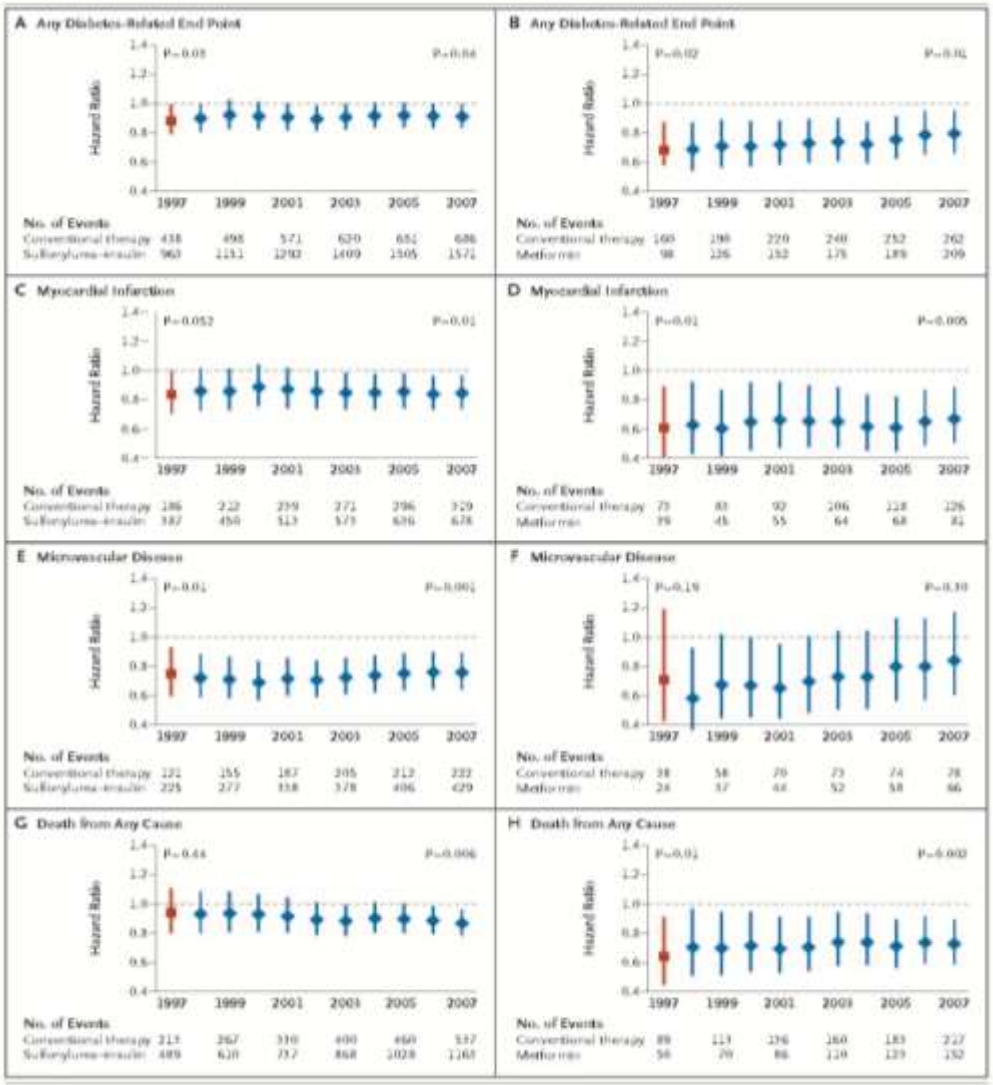
Recommendations

- 2.1.1 We recommend against more tight glycaemic control if this results in or increases the risk for severe hypoglycemic episodes (**1A**)
- 2.1.2 We recommend cautious interventions to tighten glycaemic control with the intention to lower HbA1C when values are >8.5% (69 mmol/mol) (**1C**)
- 2.1.3 We suggest cautious interventions to tighten glycaemic control with the intention to lower HbA1C when HbA1C values are >7% but <8.5% only when the projected benefits (microvascular complications) clearly outweigh the risk for hypoglycaemia, taking into account the general condition of the patient (**2D**)
- 2.1.4 We recommend intense self monitoring only to avoid hypoglycaemia in patients at risk for hypoglycaemia (2D)

Metformin Method of Action

- Increases insulin sensitivity
- Reduces glucose absorption from intestine
- Increases peripheral glucose uptake in cells
- Reduces gluconeogenesis in the liver
- Reduces weight
- Hypoglycaemia rare
- Metformin renally excreted!

UKPDS Study



- 4209 patients with Type 2 DM
- Creatinine <175 mmol/l
- Randomised to
  - Diet or
  - Insulin-sulphonylurea (normal weight)
  - Metformin (Body weight >120% IBW)

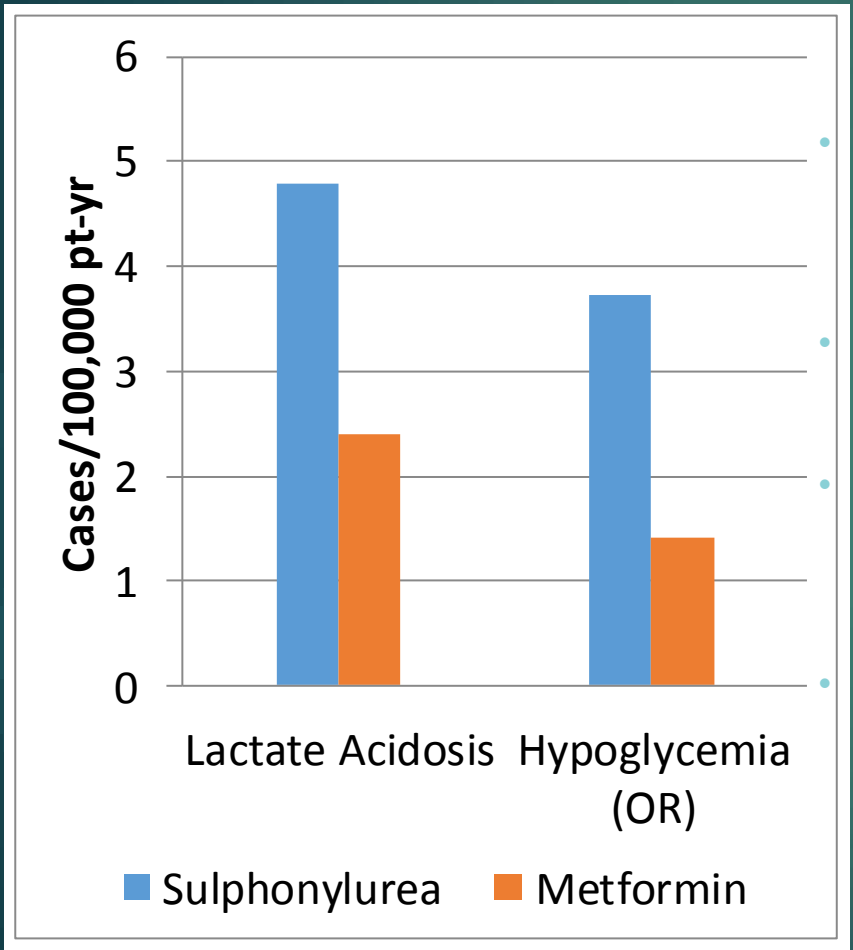
Holman NEJM 359:1577 2008

The Natural Rate of Lactate Acidosis in Type 2 DM

- Kaiser Permanente 1993-94
- No access to metformin or other biguanides
- 41,426 T2DM patient-years
- 4 certain cases, 3 probable
- All related to severe acute illness.
- 9.7-16.9/100,000 patient-years
- "Relationship may be coincidental not causal"

Brown Diabetes Care 21:1659 1998

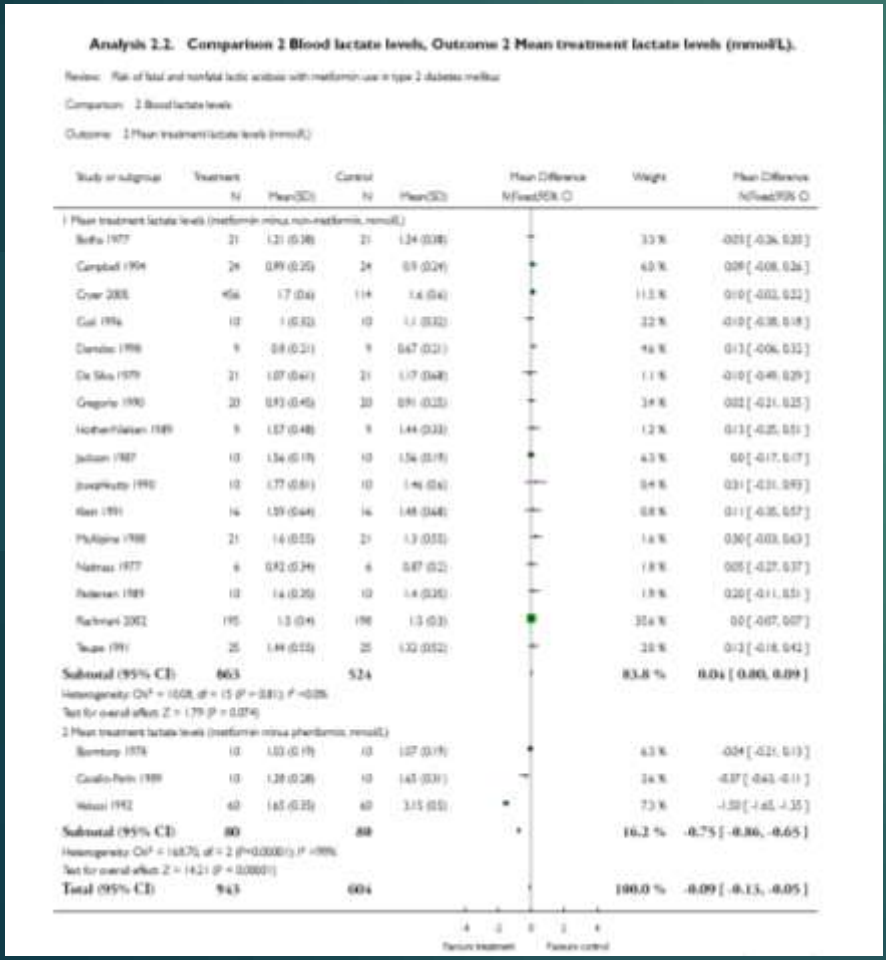
The GPRD Study



- 50,048 Type 2 DM patients in general practice
- Prospective database 1994-2006
- "There is no greater risk of lactate acidosis among metformin users"
- "Diabetes may be a leading risk factor for lactate acidosis"

Bodmer Diabetic Care 2008; 31:2086

Metformin, Lactate Acidosis & Lactate levels: Metaanalysis of RCTs



No cases of lactic acidosis in 347 studies
70,490 patient-years of metformin use

In 43% CKD was not an exclusion criterion

"There is no evidence that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate"

Saltpeter Cochrane 4:CD002967 2010

Metformin & Lactate Production

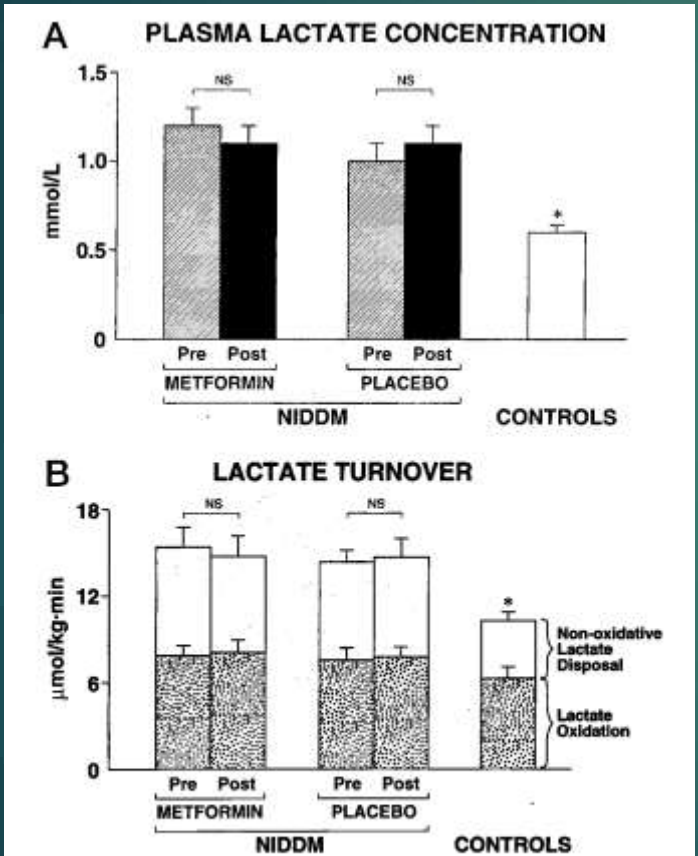


FIG. 3. Fasting plasma lactate concentration (*top*) and lactate turnover (rate of appearance; *bottom*) in controls (*open bar*) and diabetics before (*cross-hatched bar*) and after (*solid bar*) metformin or placebo therapy. *, $P < 0.01$ *vs.* both diabetic groups pre- and posttreatment.

20 Type2 DM
8 healthy controls
15 weeks RCT
Metformin vs Placebo

% gluconeogenesis from lactate and rate of lactate-derived gluconeogeneis unchanged in metformin group

Insulin clamp:
Lactate oxidation↑
Same in all groups

Curi J Clin Endocrin Metab 81:4059 1996

The Real Danger

Table 1 Predicted absolute number of deaths caused by the life-threatening complications of metformin and sulphonylureas

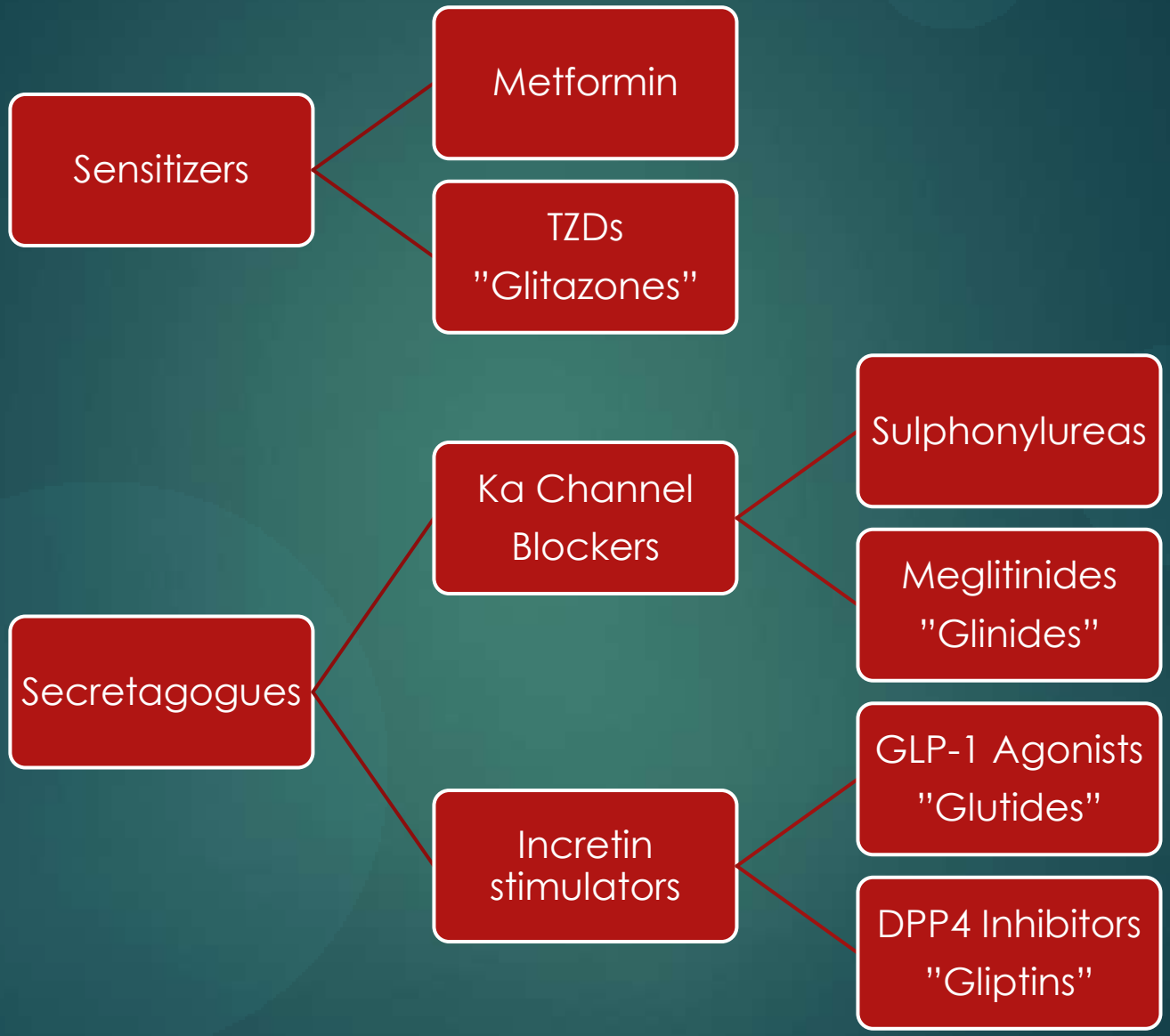
	Metformin-associated lactic acidosis	Sulphonylurea-induced hypoglycaemia	Insulin-induced hypoglycaemia
Incidence of lactic acidosis or severe hypoglycaemia in type 2 DM (number per 100,000 patient years)	6.3 [4]	1,000 [2]	1,800 [2]
Mortality (percentage; most pessimistic available figure)	50% [22]	4.3% [21]	4.3% [21]
Predicted absolute no. of deaths (number per 100,000 pt years)	3	43	77.4

Conclusion: Metformin is first choice drug in Type 2 DM and CKD

NB!

- Correct dose
- "Sick day" rules for metformin and RAS blockade

Herrington Int Urol Nephrol 40:411 2008
Heaf Perit Dial Int 34:353 2014



(SGLT2 Inhibitors → Glucosuria & Dehydration)

Oral antidiabetics in CKD

		CKD-1	CKD-2	CKD-3	CKD-4	CKD-5ND	CKD-5D
	Metformin	No adjustments		1,5g-850 mg/day*	500 mg/day**	Consider carefully/Awaiting further data	
Sulfonylureas	Chlorpropamide	No adjustments		100-125 mg/day	To be avoided		
	Acetohexamide	To be avoided					
	Tolazamide	To be avoided					
	Tolbutamide	250mg, 1-3 times/day				To be avoided	
	Glipizide	No adjustments					
	Glicazide	Start at low doses and dose titration every 1-4 weeks					
	Glyburide	To be avoided					
	Glimepiride	Recude dosage to 1 mg/day				To be avoided	
	Gliquidone	No adjustments					
Meglitinides	Repaglinide	No adjustments				Limited experience available	
	Nateglinide	No adjustments				Start at 60 mg/day	To be avoided
α-gluc inhibitors	Acarbose	No adjustments			Avoid if GFR<25mL/min	To be avoided	
	Miglitol	Limited experience available					
	Pioglitazone	No adjustments					
DPP-IV inhibitors	Sitagliptin	No adjustments		Reduce to 50 mg/day	Reduce to 25 mg/day		
	Vildagliptin	No adjustments		Reduce to 50 mg/once daily			
	Saxagliptin	No adjustments		Reduce to 2,5 mg/once daily			
	Linagliptin	No adjustments					
	Alogliptin	No adjustments		Reduce to 12,5 mg/daily			
Incretin Mimetics	Exenatide	No adjustments	Reduce dose to 5 mcg/once to twice daily		To be avoided		
	Liraglutide	Limited experience available					
	Lixisenatide	No adjustments	Careful use if GFR 80-50 mL/min				No experience available
	Pramlintide	Limited experience available					
SGLT-2 inhibitors	Dapagliflozin	Limited experience available					
	Canagliflozin	Reduced efficacy		Careful monitoring		To be avoided	
	Empagliflozin	Limited experience available					

FIGURE 2: Suggested use and dose adaptation of glucose-lowering drugs according to the CKD stages (see also Table 1 for details). *1.5 g with eGFR > 45 mL/min and 850 mg with eGFR 30–45 mL/min; **to be temporarily witheld in periods of unstable eGFR.

Arnauts NDT 2014

Sulphonylureas in CKD

	SU	Patients	No. (A/C)	Type	Control	Result
Weir 2011	Glyburide	CKD	354/1290	Case control	Metformin & Insulin	Lower risk (50%) of hypoglycemia than insulin
Türk 2008	Gliquidone	NODAT	47/0	Retro-spective	No	FBG 8.6→6.7 mM 8% Hypoglycemia
Holstein 2010	All	CKD/Normal with Hypoglycaemia	139	Retro-spective	NonCKD	73% of cases had CKD 27% Rx with interacting drugs -Clopidogrel -Phenprocoumon -Diclofenac -Phenytoin -Fluvastatin

CKD: Chronic Kidney Disease
NODAT: New onset diabetes after transploantation
FBG: Fasting blood glucose
A/C: Active/Controls

Thiazolidinediones (TZDs) "Glitazones"

- Peroxisome proliferator-activated (PPAR) γ receptor activators
- Reduce insulin resistance
- Antiproliferative
- Antiinflammatory
- Leptin ↓→Appetite ↑

- Registration difficulties (heart failure, hepatitis, bladder cancer)

Glitazones in CKD

Author	Pts.	No	Drug	Time (mths)	Factor	Change	Side Effects	Other
Abe 2008	HD	31	Pioglitazone	6	Hb A1c	-1.1***	No	Triglyc↓ BP↓
Luther 2004	RT	10	Pioglitazone	8	Hb A1c	-1.3*	No	
Abe 2010	HD	63	Pioglitazone	21	Hb A1c	-0.6***	No	CRP↓ Adiponectin↓
Luther 2004	RT	10	Pioglitazone	8	Hb A1c	-1.3*	No	
Agarwal 2005	CKD	301	Rosiglitazone	6	Hb A1c	-1.1**	No	
Akcay 2009	PD	24	Rosiglitazone	12	Hb A1c	-0.5***	No	Echocardiography unchanged
Van Hooland 2009	PD	12	Rosiglitazone	1			Oedema	Peritoneal transport↑ BP↓
Chiang 2007	HD	78	Rosiglitazone	15	Hb A1c	-1.5**	No	
Pietruck	RT	21	Rosiglitazone	2	Hb A1c	-0.4[?]	Oedema	BP↓
Villanueva 2005	RT	8	Rosiglitazone	12	Insulin Rx	-75% pts.	Oedema	
Voytovitch 2005	RT	10	Rosiglitazone	1	Glucose	-0.6 mmol/l**	No	Endothelial function↑
Wong 2005	PD	52	Rosiglitazone	6	Insulin Rx	-6 IU/d***		
Mohideen	HD	12	Troglitazone	6	Insulin Rx	-13 IU/d*	No	
Kurian 2008	RT	46	TZD	16	Hb A1c	-0.5	No	
Manley 2003	HD	40	TZD	3	Hb A1c	-0.6	No	BP↓

*:p<0.05
**:p<0.01
***:p<0.001

Glitazones and Mortality

Author	Pts.	No	Drug	Time (mths)	Factor	Change
Brunelli 2009	CKD	91	TZD	12	Death risk	-Insulin 0.53* +Insulin 0.82
Ramirez 2009	HD	2393	Rosiglitazone	13	CV Death Risk	1.59**
Schneider 2008	CKD	597	Pioglitazone	36	Death + AMI + Stroke	0.60*

DPP4 Inhibitors in CKD "Gliptins"

Author	Pts.	No	Drug	Time (mths)	Factor	Subsets	Change	Side Effects
Chan 2008	CKD	91	Sitagliptin	12	Hb A1c		-0.8?	No
Lukashevich 2011	CKD	525	Vildagliptin	6	Hb A1c	GFR 30-50 GFR <30	-0.5*** -0.6***	No
Nowicki 2011	CKD/ ESRD	170	Saxagliptin	12	Hb A1c	GFR 30-50 (90 pts.) GFR <30 (41) ESRD (39)	-0.7*** -0.3? -0.1	No
Lane 2011	NODAT	15	Sitagliptin	3	Hb A1c		-0.5**	No

*:p<0.05
**:p<0.01
***:p<0.001

GLP-1 agonists & CKD

Author	Pts.	No. (A/C)	Drug	Time (mths)	Control	Change	Other Effects
Davidsen 2011	CKD	63/13	Liragutide	6	Placebo & normal renal function	-1.3*	Weight↓ BP↓ Increased risk of nausea (19%) & hypoglycaemia (17%) vs. Normals

*:$p<0.05$

Conclusions

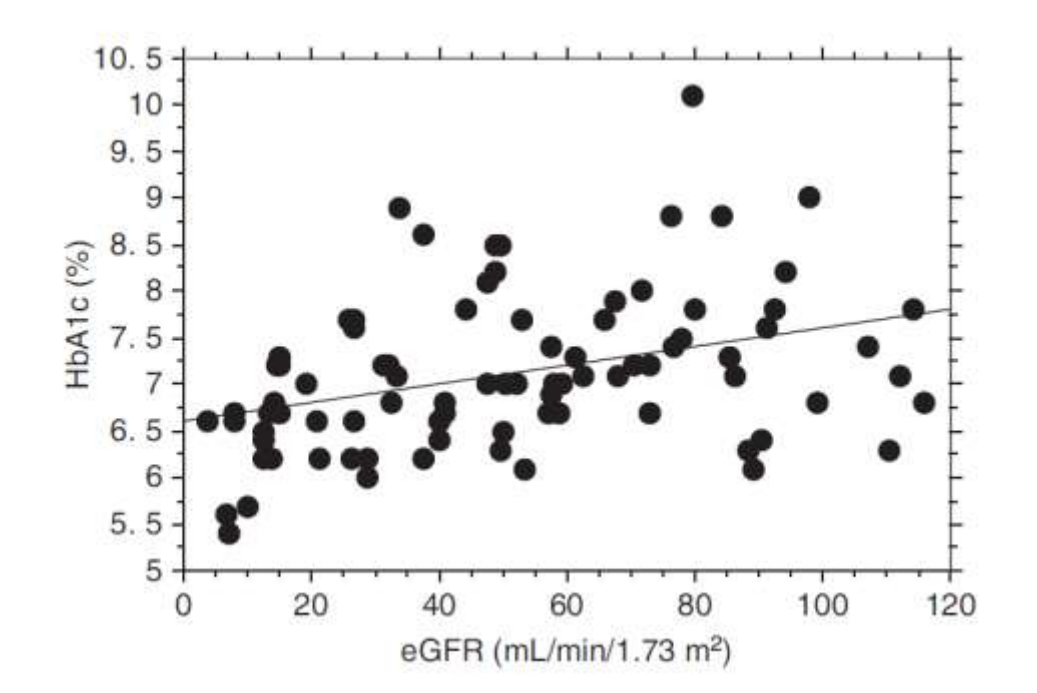
- ESRD is a prediabetic condition
- Unambitious target in ESRD: <8.5%
- Metformin first choice
- Choice of second non-insulin drugs determined mainly by price & side effects
- My personal choices:
  - SUs: Glipizide (Mindiab®), gliquidone (Glurenorm®)
  - Glitazones: Pioglitazone (Actos®)
  - Gliptins: Linagliptin (Trajenta®)
  - GLP-1 Analogues: no
  - SGLT2 Inhibitors: no

TZDs, GLP-A & DPP4-I

Drug Name	Commercial Name	Typical Side Effects	Dose reduction in CKD
Thiozolidinediones (TZD) (oral) PPARγ Agonists			
Pioglitazone	Actos	Oedema, hypoglycaemia, weight↑, GI, (bladder cancer)	No
(Rosiglitazone)		Withdrawn from many markets (CV toxicity?)	No
GLP Analogues (s.c.)			
Exanatide	Byetta	Hypoglycaemia, Nausea, GI Symptoms, Headache, (pancreatitis, AKI)	No (Caution/ No evidence)
Liraglutide	Victoza		
Lixisenatide	Lyxumia		
DPP4 Inhibitors (oral)			
Sitagliptin	Januvia	Hypoglycaemia, Nausea, GI Symptoms, Oedema, Headache Rash (pancreatitis)	Yes
Vildagliptin	Galvus		Yes
Saxagliptin	Onglyza		Yes
Linagliptin	Trajenta		No
Combination with metformin	Eucreas, Janumet, Jentadueto, Komboglyze		To be avoided

HbA_{1c} is significantly correlated to eGFR

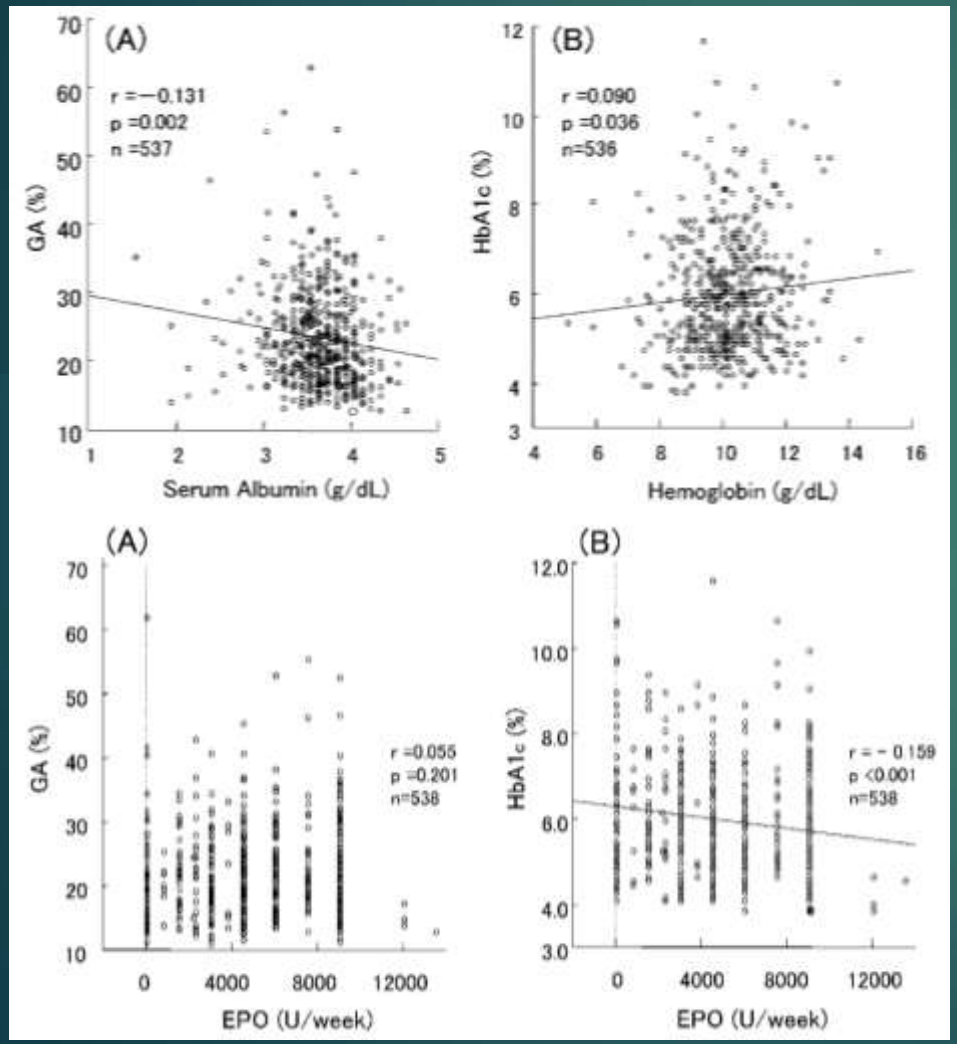
- Mean HbA_{1c} [eGFR <30 ml/min] 6.3% ±0.5% B-Glucose 9.1 mmol/l
- Mean HbA_{1c} [eGFR >60 ml/min] 7.4% ±0.8% B-Glucose 9.3 mmol/l



K. Shima; Ann Clin Biochem; 2012, vol. 49, 68-74

With thanks to Rikke Borg

Hb, EPO & Hb A1C



538 DM HD pts.
828 NonDM HD pts.
365 DM normal renal function

Inaba JASN 18:896 2007

Glucagon

Normal

ESRD Normal OGT

ESRD Impaired OGT

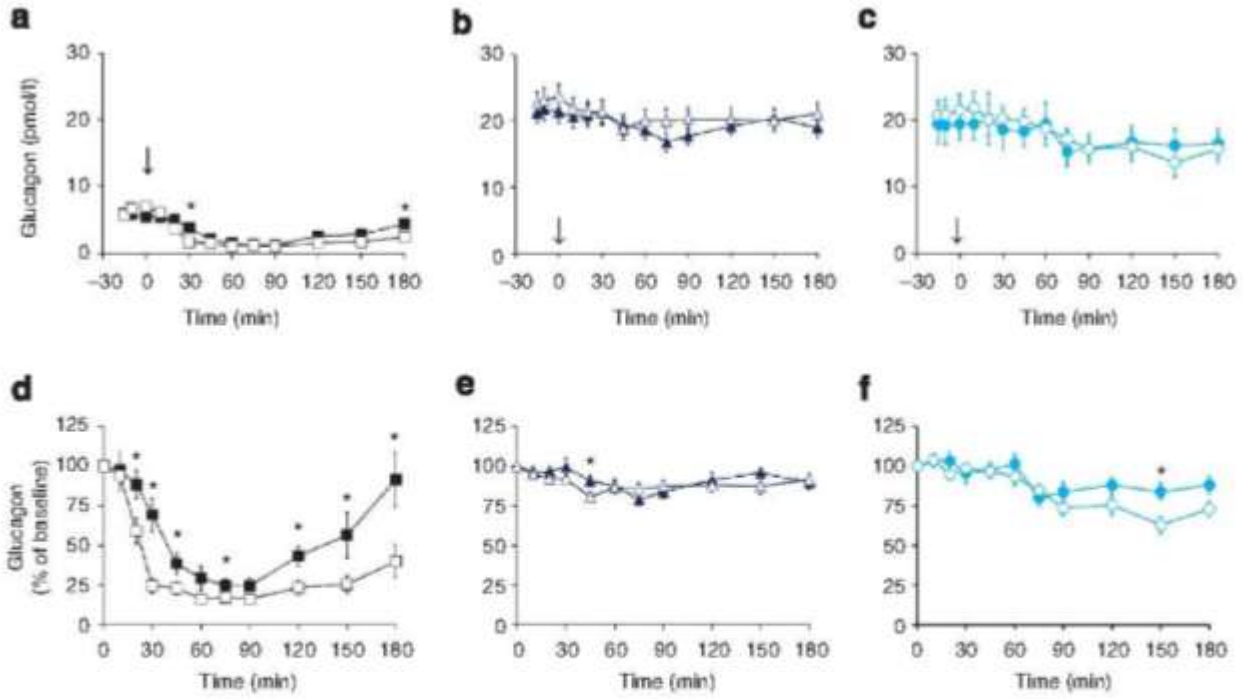


Figure 6 | Glucagon. Glucagon responses during oral glucose tolerance test (filled symbols) and isoglycemic intravenous glucose infusion (open symbols) in control subjects (**a** and **d**) and in patients with end-stage renal disease and normal glucose tolerance (**b** and **e**) or impaired glucose tolerance (**c** and **f**). Illustrated as absolute responses (**a**-**c**) and relative responses (% of baseline) (**d**-**f**). Data are mean ± s.e.m. Asterisks (*) indicate significant ($P < 0.05$) differences at individual time points, and arrows (↓) indicate time of initiation of oral glucose ingestion.

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Meglitinides

- Ka-channel blockers (different receptor than SUs)
- Repaglinide & Netaglinide
- Lower rate of hypoglycaemia than SUs?
- More expensive than SUs
- Increase insulin secretion → Burnout
- Repaglinide: dose reduction in CKD

Meglitinides in CKD

	Drug	Patients	No. (A/C)	Type	Control	Result
Türk 2006	Repaglinide	NODAT	23/21	Control	Rosi-glitazone	HbA1c 7.6→5.8% 39% switched to insulin Similar to rosiglitazone 8% nausea/diarrhea
Voytovich 2007	Nateglinide	NODAT	14/0	Prospective	No	2-week Rx 2-hr BG 10.5→7.6 Late insulin response↑
Sun 2009	Glitinides	HD	68/34	Control	Insulin	34% risk of hypoglycaemia compared to insulin
Abe	Mitiglinide	HD	31	Prospective	No	HbA1c 7.0→5.9% FBG 9.4→8.3 mM No side effects

CKD: Chronic Kidney Disease
NODAT: New onset diabetes after transploantation
FBG: Fasting blood glucose
A/C: Active/controls