Modern Guidelines Methodology

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

randomised controlled trials. The relevance to parachute use is that individuals jumping from aircraft without the help of a parachute are likely to have a high prevalence of pre-existing psychiatric morbidity. Individuals who use parachutes are likely to have less psychiatric morbidity and may also differ in key demographic factors, such as income and cigarette use. It follows, therefore, that the apparent protective effect of parachutes may be merely an example of the "healthy cohort" effect. Observational studies typically use mul-

Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Contributors: GCSS had the original idea. JPP tried to talk him out of it. JPP did the first literature search but GCSS lost it. GCSS drafted the manuscript but JPP deleted all the best jokes. GCSS is the guarantor, and JPP says it serves him right.

BMJ 327:1459 2003

PICO Studies

P	**P**atient, Population, or Problem	How would I describe a group of patients similar to mine?
I	**I**ntervention, Prognostic Factor, or Exposure	Which main intervention, prognostic factor, or exposure am I considering?
C	**C**omparison or Intervention (if appropriate)	What is the main alternative to compare with the intervention?
O	**O**utcome you would like to measure or achieve	What can I hope to accomplish, measure, improve, or affect?
	What type of question are you asking?	Diagnosis, Etiology/Harm, Therapy, Prognosis, Prevention
	Type of study you want to find	What would be the best study design/methodology?

ERBP DM ”P”:
Patients with CKD 3-5 and Diabetes Mellitus

ERBP DM Outcomes

Survival/mortality
Progression to end-stage kidney disease
Quality of life
Myocardial infarction
Stroke
Amputation
Loss of vision
Hospital admissions
Deterioration of residual renal function when already on dialysis
Patient satisfaction
Minor mobid events
Hypoglycemia
Delayed wound healing
Infection
Visual disturbances
Pain
Functional status
Hyperglycemia
Glycemic control
Glycated hemoglobin
Self-measurement
Access to transplantation
Survival of the technique
Cancer
Need for temporary hemodialysis catheter
Infections of the vascular access
Keto-acidosis
Weight change
Symptom control: dyspnea, chest pain
Sudden death
Rhabdomyolysis
Depression symptoms
Exercise capacity
Insuline sensitivity
Adherence to treatment strategy
Blood pressure
Proteinuria
Need for blood transfusion
Bleeding: highly important

ERBP Process

1. Which questions shall we ask? On-line questionnaire to all ERA-EDTA members
2. Definition of program
3. Abstract review of all relevant articles
4. Selection of all articles with PICO structure
5. Detailed review of these articles
6. Statistical analysis
7. ”GOBRAT”
8. Repeat 3-7

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ERBP DM Questions

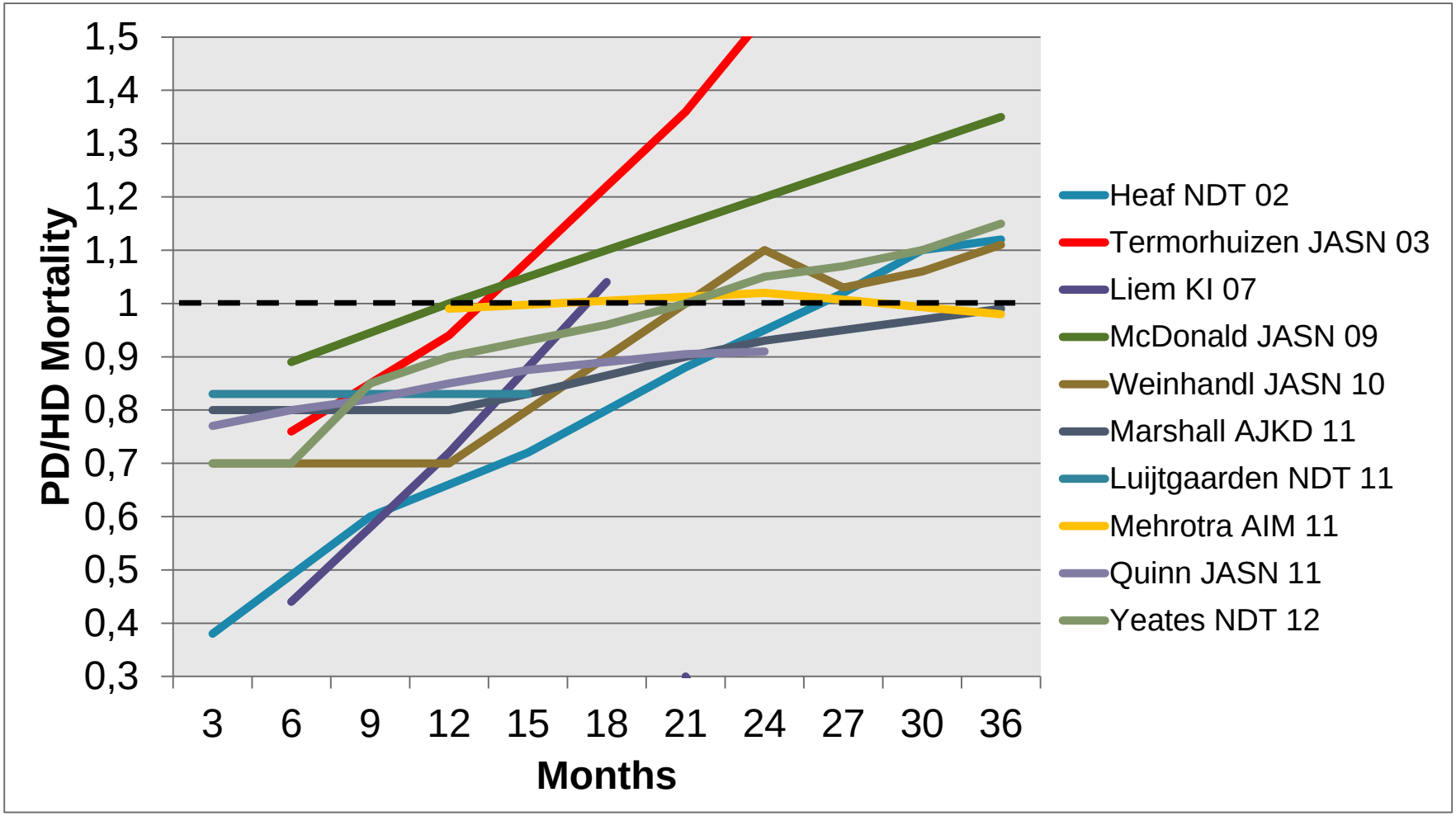
- **Treatment modality: Should patients with CKD stage 5 and diabetes mellitus start with peritoneal dialysis or hemodialysis as a first modality?**
- **Treatment modality: should diabetics start dialysis earlier, i.e. before becoming symptomatic, than non-diabetics?**
- **Vascular access: In patients with CKD stage 5 and diabetes mellitus, should a native fistula, a graft or a tunnelled catheter be preferred as initial access?**
- **Access to transplantation: What is the current access to the waiting list for dialysis patients with diabetes mellitus compared to patients without diabetes?**
- **Access to transplantation: : What is the benefit of renal transplantation for dialysis patients with diabetes mellitus?**
- **In patients with renal failure(eGFR <45 mL/min/1.73m^2) or on dialysis, and diabetes mellitus should we aim to lower HbA1C by more tight glycaemic control**
- **In patients with renal failure (eGFR <45 mL/min/1.73m^2) or on dialysis and with diabetes mellitus, are there better alternatives than HbA1c to estimate glycemic control?**
- **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?**
- **In patients with renal failure (eGFR < 45mL/min/1.73m^2), is maximal oral therapy better than starting/adding insulin in an earlier stage?**
- **Is any oral drug superior to another in terms of mortality/complications/glycemic control in diabetic patients with renal failure (eGFR <45 mL/min/1.73m^2) or on dialysis?**
- **Access to transplantation: : What is the benefit of renal transplantation for dialysis patients with diabetes mellitus?**
- **In patients with renal failure (eGFR <45 mL/min/1.73m^2) and diabetes and coronary artery disease, is PCI or CABG or conservative treatment to be preferred?**
- **In patients with renal failure (eGFR <45 mL/min/1.73m^2 or on dialysis) and diabetes should we prescribe Beta Blockers to prevent sudden cardiac death**
- **In patients with renal failure (eGFR <45 mL/min/1.73m^2 or on dialysis) and diabetes, should we prescribe lipid lowering therapy in primary prevention? IIIQ4a Should we recommend interventions aimed at increasing energy expenditure and physical activity in patients with renal failure (eGFR <45 mL/min/1.73m^2 or on dialysis) and diabetes?**
- **Should we recommend interventions aimed at reducing energy intake in patients with renal failure (eGFR <45 mL/min/1.73m^2 or on dialysis) and diabetes?**
- **Should antiplatelet therapy be recommended in patients with renal failure (eGFR <45 mL/min/1.73m^2 or on dialysis) and diabetes, regardless of their cardiovascular risk?**

Q1 Treatment modality: Should patients with CKD stage 5 and diabetes mellitus start with peritoneal dialysis or hemodialysis as a first modality?

Recommendations

- In view of the absence of evidence of superiority of one modality over the other in CKD5 patients with diabetes, we recommend to give priority to patient preference (1C).
- Providing patients with unbiased information about the different available treatment options is therefore indispensable.

HD vs. PD: Status 2013

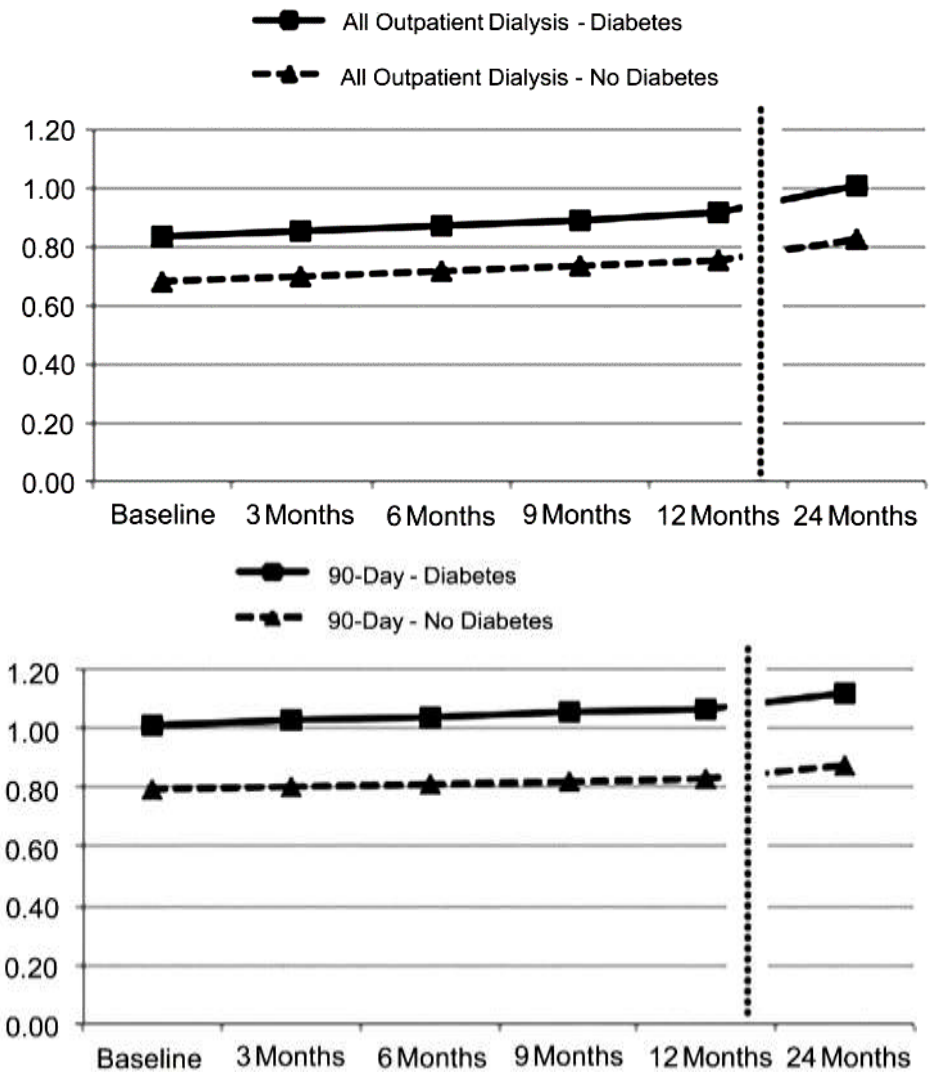


Subgroups: Where is PD best?

	No. Studies
Young better than Old	12/12
Male better than Female	6/7
Non-DM better than DM	16/18
No comorbidity better than Comorbidity	9/9

25 studies 1995-2011,
11 geographical populations

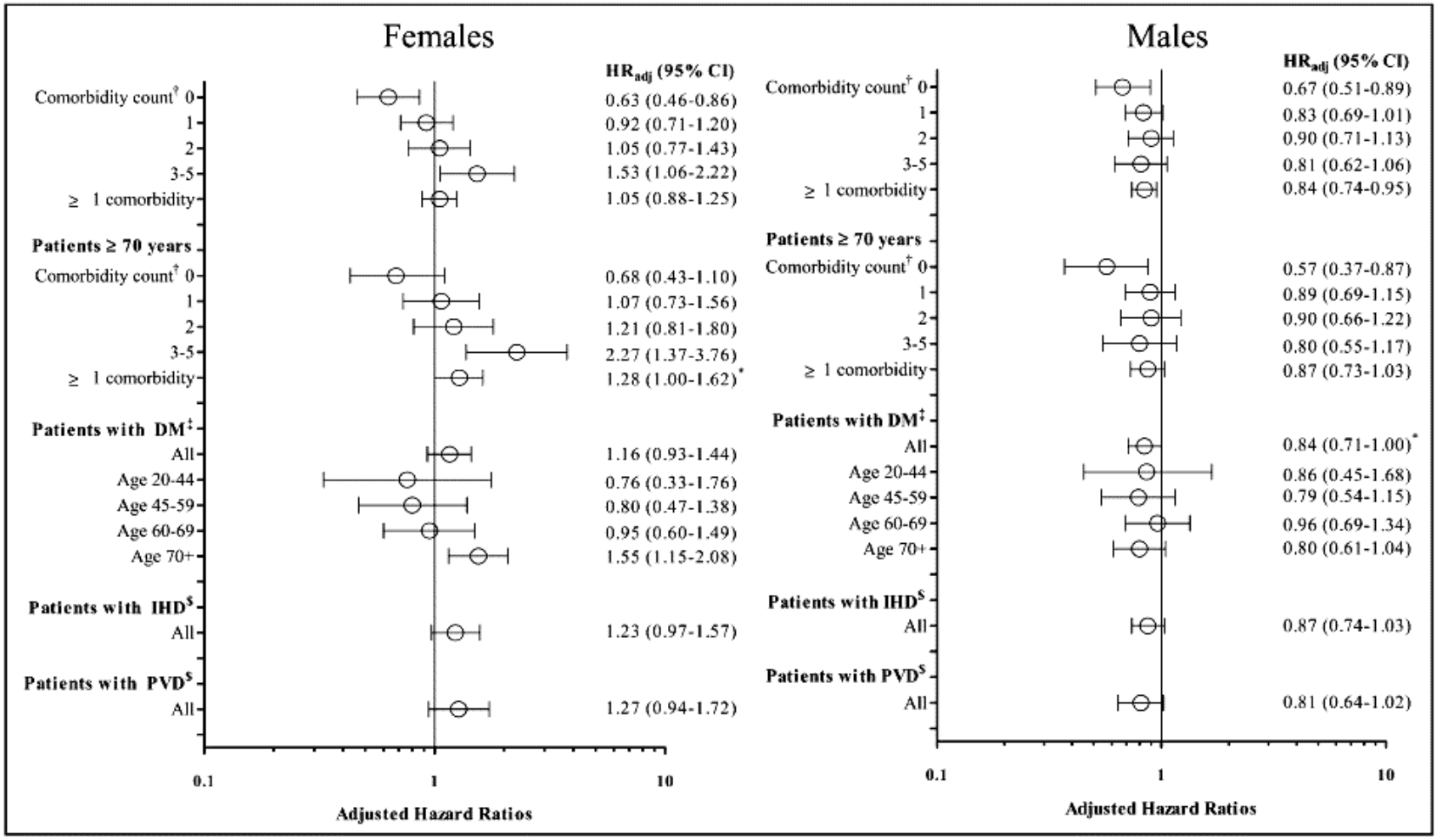
DM vs. Non-DM: Canada



Quinn JASN 22:1534 2011

HD vs. PD: Subgroups

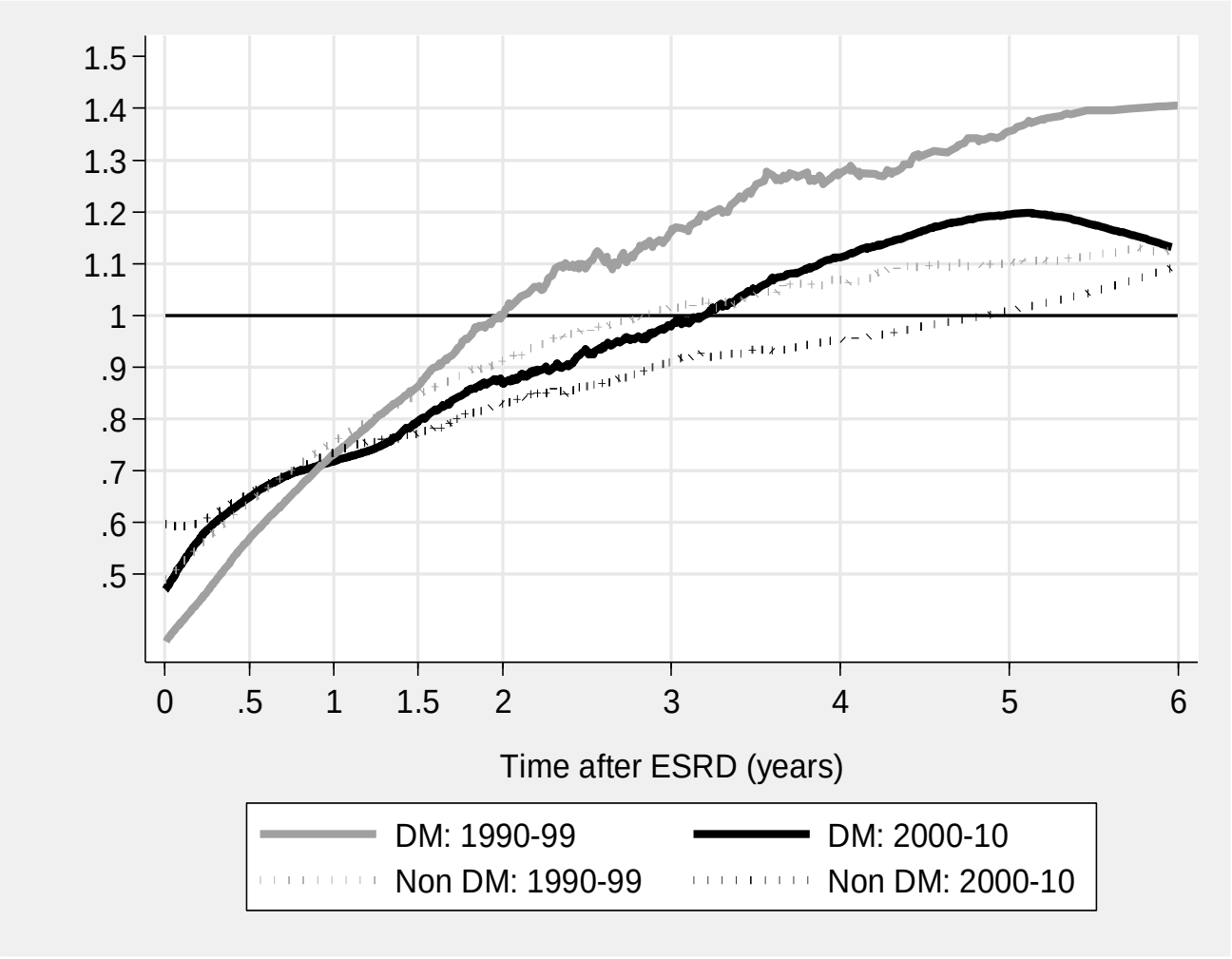
ERA-EDTA Registry



PD better HD better

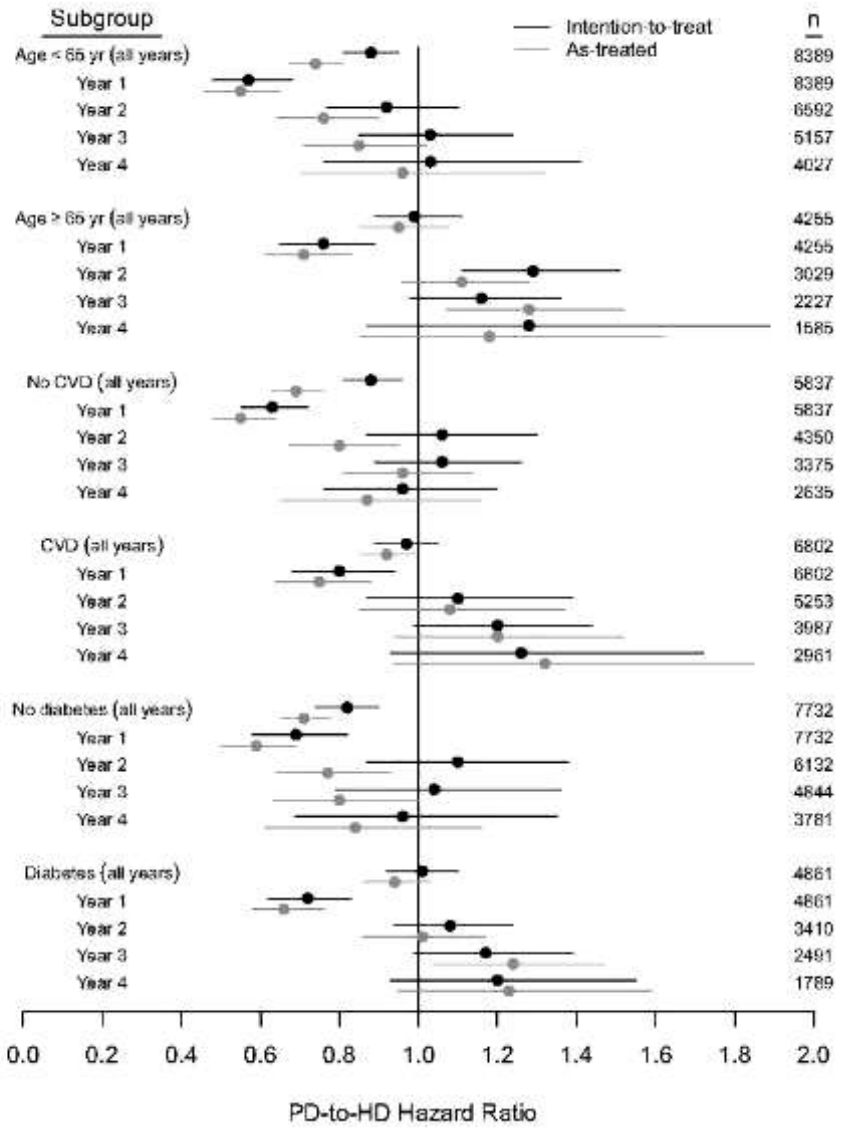
Luijtgaarden NDT 26:2940 2011

PD & Diabetes: Denmark



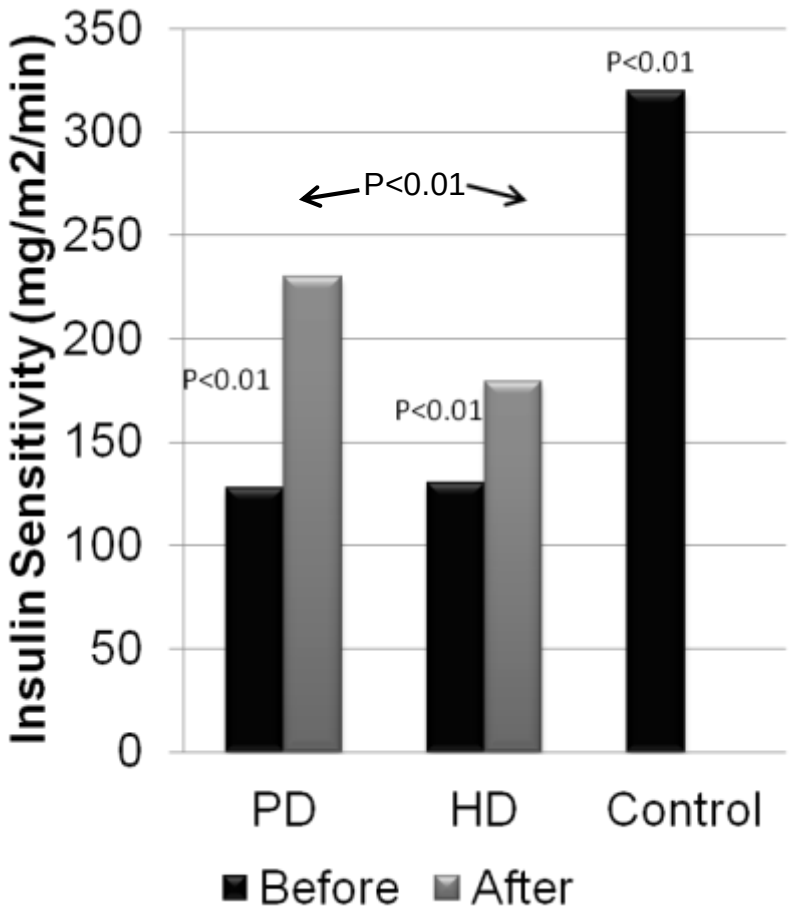
Denmark 1990-2010

Day 90 Analysis



Weinhandl JASA 21:499 2010

Insulin Sensitivity: PD vs. HD

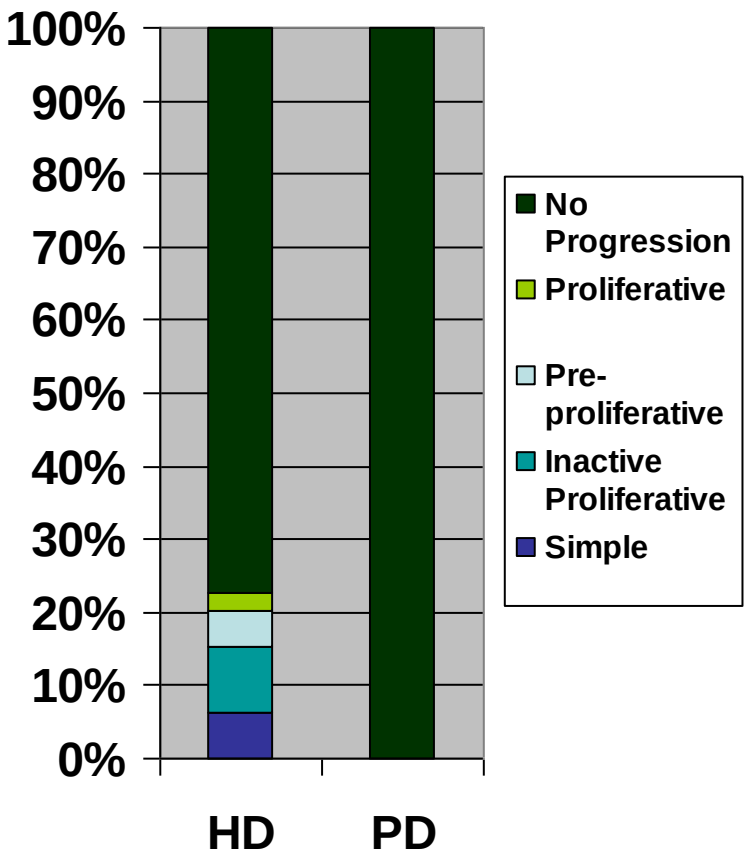


- 7 incident HD, 7 PD and 7 controls
- 3 months Rx
- No difference in dialysis dose (PD 2.1/week, HD 1.2/HD)
- No difference in GFR, nutrition
- Initial higher fasting glucose (98 vs. 88 mg%), but normal insulin levels
- Hyperglycaemic clamp before and after
- PD 80% rise in insulin sensitivity. HD 38% ($p<0.01$)

Mak Ped Res 40:304 1996

PD and Diabetic Retinopathy

- 79 HD, 27 PD patients
- Follow-up 1 year
- 23% with retinopathy progression in HD vs. 0% in PD patients



P<0.01

Kuriyama PDI 27S2:190 2006
Sato Clin Dial 16:2137 2000

The Perfect Diabetic ESRD Clinician

Upon initiation of dialysis care: first 90 days	
Formulate comprehensive plans of care for initiation of dialysis Collaborate with nephrologist Collaborate with dialysis team Collaborate with dietitian Collaborate with social worker	Care plan shall include: Quality of life goals Dialysis prescription (HD and PD) If PD and prescribing icodextrin: explain and assure that glucometer and test strips must be compatible with icodextrin PET Profile Access care: If HD, assure AVF is constructed and assure positive progress toward maturation If PD, assure that PD catheter access is adequately disinfected daily with chlorhexidine swipe and assure exit site antibiotic prophylaxis Preservation of residual renal function BP target: means and cautions Pulse pressure target: means and cautions Glucose targets: means and cautions Lipid targets: means and cautions Cardiac care in relation to modality, esp. HD Vascular care Nutritional optimization in relation to modality Eye care Foot care Mobility assessment and needs Rehab/physical therapy assessment and needs Activities of daily living and support system Participate in initial 30 day dialysis team care plan
Broad-based patient education Collaborate with dietitian and dialysis team	Explain comprehensive care plans for dialysis care: Clearance goals: dialytic Kt/V; residual Kt/V Modality specific features to achieve clearance Modality specific features for fluid management Glucose, phosphorus, calcium, PTH, albumin, lipid, potassium, and hemoglobin targets BP and pulse pressure targets Cardiac care in relation to modality Peripheral vascular care and concerns Glycemic monitoring daily with diary Explain meal planning and timing Explain glycemic control medications, actions, and timing in relation to modality Educate regarding HD session, meal timing, insulin actions and timing Educate regarding PD associated glucose influx, percent dextrose, insulin actions and timing Explain and assure that glucometer and test strips must be compatible with icodextrin Explain collaboration with dietitian, dialysis team, MDs Utilize reading materials; include family members
Glycemic care Weekly during first 30 days May space to bi-weekly as glucose pattern comes into target zone and stabilizes	Establish or reinforce daily glucose monitoring patterns Counsel that insulin or oral hypoglycemic dosing will require adjusting as GFR declines Avoid metformin and be wary of sulfonylureas Adjust medications in collaboration with endocrinologist and/or nephrologist Assure and coach regarding optimal use of basal-bolus-correction insulin Rx Review glucose diary at weekly and monthly sessions Review and discuss glucose trends and patterns: evaluate why pattern may not be optimal If HD, evaluate pattern in relation to HD sessions and meals on HD days If PD, may initiate icodextrin in long dwell If PD, evaluate pattern of glucose in relation to dextrose in PD and timing of PD dwell Refine B-B-C insulin or oral hypoglycemic dosing as glucose patterns require to achieve glucose targets Review diet in relation to glucose patterns; educate and counsel Collaborate as needed with endocrinologist and dietitian
Lipid care Quarterly	Assess lipid panel quarterly Collaborate with nephrologist, endocrinologist for Rx Employ lipid lowering therapy to achieve LDL < 100 mg/dl and triglycerides < 150 mg/dl Monitor CPK and liver quarterly if Rx employed
Blood pressure care Weekly	Explain rationale, actions, side-effects of BP medications Explain role of salt and salt restriction Examine for edema weekly Adjust target dry weight carefully so that intradialytic (HD) hypotension is minimized but end-of-dialysis or daily BP is < 130/80 mmHg but not lower than 100–110 systolic or 60 diastolic Titrate medications to achieve and maintain BP < 130/80 and pulse pressure < 40 mmHg as dry weight is established Collaborate with nephrologist Encourage and enable home BP monitoring as feasible
Cardiac profiling and care Examine heart weekly	Explain cardiac risks, signs, symptoms Cardiac exam—at each weekly encounter Focus on heart rate, pulse pressure, rhythm Cardiac echo—obtain in first 90 days to compare with pre-ESRD echo

Upon initiation of dialysis care: first 90 days	
	Electrocardiogram—obtain in first 90 days to compare with pre-ESRD ECG Collaborate to assure optimal cardiac primary prevention Rx is in place
Vascular profiling and care Examination to establish ESRD Baseline	Explain vascular risks, signs, symptoms Carotid exam—note bruit or not Aortic exam—note bruit or not; note width if feasible Iliac—femoral exam—note bruit or not Discuss signs and symptoms of peripheral ischemia Foot exam—note evidence for vascular insufficiency Pedal pulse Capillary refill time Skin color and atrophy Hair patterns Toe, ball, heel dermal health Refer for Doppler and ankle/brachial Index if any evidence for peripheral insufficiency exists Emphasize podiatry collaboration as needed
Therapy aimed at calcium, phosphorus, PTH Bi-weekly, then monthly Collaborative Intends to mitigate calcification	Counsel regarding calcium, phosphorus, PTH targets Counsel regarding diet phosphorus restriction Utilize phosphorus binder therapy: counsel regarding timing: titrate to target monthly Counsel regarding oral calcium intake restrictions Utilize vitamin D Rx: titrate to target PTH monthly
Re-asses and re-formulate comprehensive plans of care at the 90-day time interval Collaborate with nephrologist Collaborate with dialysis team Collaborate with dietitian Collaborate with social worker	New Care plan shall include: Quality of life interval assessment Mobility reassessment and needs Activities of daily living reassessment Dialysis prescription (HD and PD) If PD and prescribing icodextrin: check utilization and achieved Kt/V PET profile and Its impact on glycemic control and BP control If HD: achieved Kt/V Preservation of residual renal function Access care If HD, assure AVF is constructed and assure positive progress toward maturation If PD, assure that PD catheter access is adequately disinfected daily with chlorhexidine swipe and assure exit site antibiotic prophylaxis Achieved BP and patterns of hypotensive and hypertensive episodes: assess why and correct Achieved pulse pressure: assure PP < 40 mmHg Achieved glycemic control If HD, assess patterns on HD days vs. non-HD days If PD, assess patterns during day vs. overnight, and assess patterns in relation to icodextrin (when appropriate) and in relation to percent dextrose used Note major trends, problems, and formulate corrective plans to implement Assure and coach regarding optimal use of basal-bolus-correction insulin Rx Evaluate heart rates, echo, ECG in relation to pre-ESRD data and formulate optimal preventative care collaboratively to implement Evaluate peripheral vascular condition and formulate optimal preventative care collaboratively to implement Evaluate nutritional parameters collaboratively and formulate plan for adjustments and provide reinforcing counsel along with dietitian; in particular provide counsel regarding meals and glycemic control Participate in initial 90-day dialysis team care plan

ESRD, end-stage renal disease; CKD, chronic kidney disease; BP, blood pressure; HD, hemodialysis; PD, peritoneal dialysis; AVF, arteriovenous fistula.

Dialysis: The first 90 days

Mahnensmith Semin Dial 23:206 2010

Diabetes Care & Education: Does it help?

- 83 dialysis DM patients (T1DM 87%, PD 16%)
- RCT: Intensive Care vs. Standard Care
- 12 months

	Standard	Intensive
Foot risk score	3.3	2.0*
Amputations	5	0*
Vascular Hospitalisations	10	1**
Hb A1C%	7.2	6.3**
QOL	76	86***

A program of intensive diabetes education and care management in a dialysis unit is effective in providing significant improvements in patient outcomes, glycemic control, and better quality of life in patients with diabetes mellitus.

McMurray AJKD 40:566 2002

Treatment modality: should diabetics start dialysis earlier, i.e. before becoming symptomatic, than non-diabetics?

- **Recommendations**
- We recommend initiation of dialysis in diabetic patients is started on the same criteria as in non diabetic patients (**1A**)
- We suggest to timely create vascular access in patients considering HD as RRT as maturation of AV fistula might be delayed (**2D**)

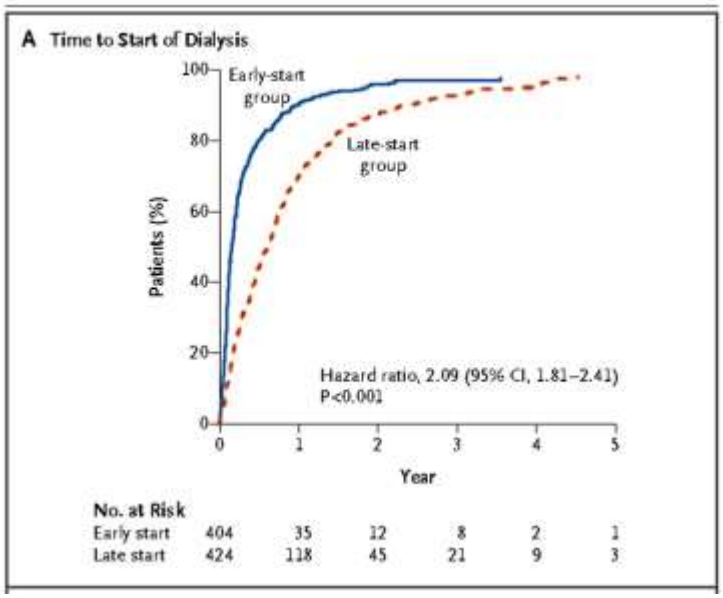
IDEAL Study: Design

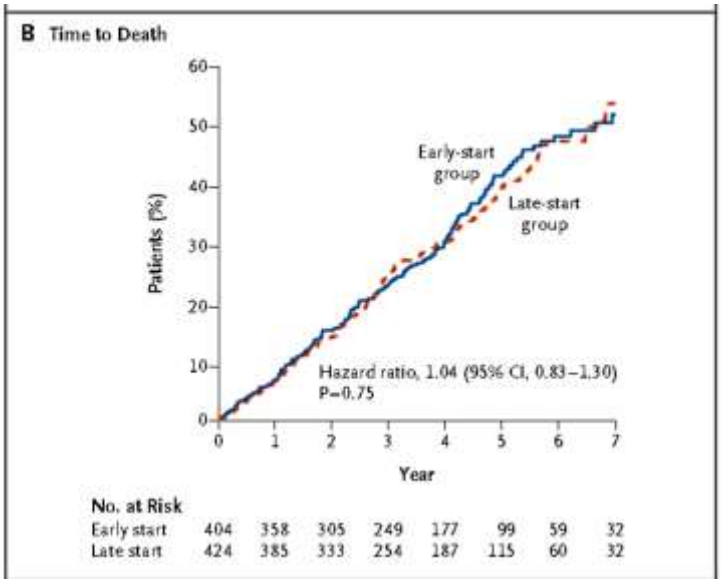
	Early Start	Late Start
No. Patients	404	424
Target start (ml/min/1.73 m^2) (CG Creatinine Clearance)	10-15	5-7
Time to dialysis start (months)	1.8	7.4
Achieved Start (CG Cr Cl)	12.0	9.8
Achieved start (MDRD eGFR)	9	7.2
Start > 7 ml/min (CG Cr Cl)		76%
Acute dialysis access	3.7%	8.3%

CG = Cockcroft-Gault Creatinine Clearance

Cooper NEJM 363:609 2010

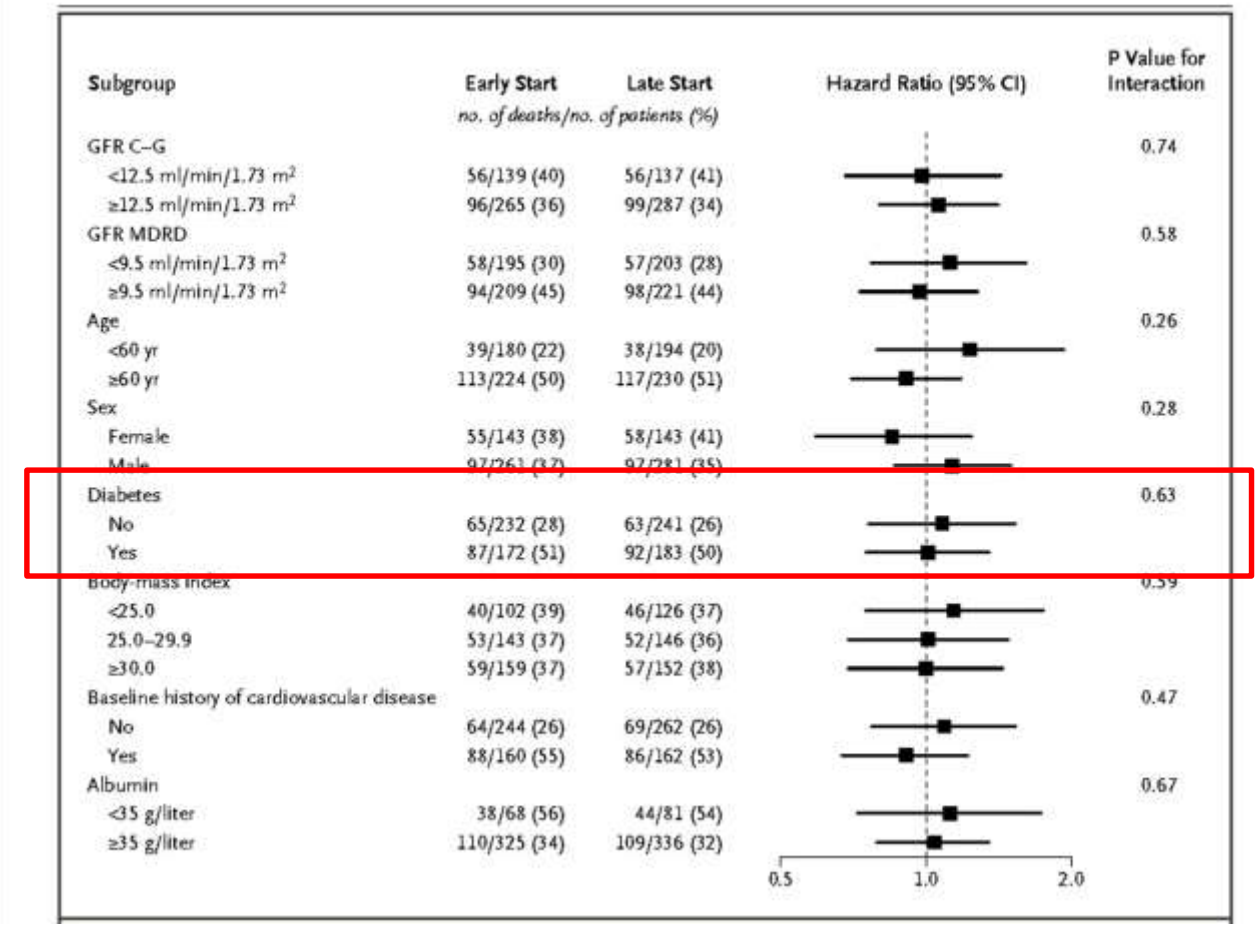
IDEAL Study: Results





Cooper NEJM 363:609 2010

IDEAL Study: Subanalysis



Subgroup	Early Start	Late Start	P Value for Interaction
	no. of deaths/no. of patients (%)		
GFR C–G			0.74
<12.5 ml/min/1.73 m²	56/139 (40)	56/137 (41)	
≥12.5 ml/min/1.73 m²	96/265 (36)	99/287 (34)	
GFR MDRD			0.58
<9.5 ml/min/1.73 m²	58/195 (30)	57/203 (28)	
≥9.5 ml/min/1.73 m²	94/209 (45)	98/221 (44)	
Age			0.26
<60 yr	39/180 (22)	38/194 (20)	
≥60 yr	113/224 (50)	117/230 (51)	
Sex			0.28
Female	55/143 (38)	58/143 (41)	
Male	97/261 (37)	97/281 (35)	
Diabetes			0.63
No	65/232 (28)	63/241 (26)	
Yes	87/172 (51)	92/183 (50)	
Body-mass index			0.59
<25.0	40/102 (39)	46/126 (37)	
25.0–29.9	53/143 (37)	52/146 (36)	
≥30.0	59/159 (37)	57/152 (38)	
Baseline history of cardiovascular disease			0.47
No	64/244 (26)	69/262 (26)	
Yes	88/160 (55)	86/162 (53)	
Albumin			0.67
<35 g/liter	38/68 (56)	44/81 (54)	
≥35 g/liter	110/325 (34)	109/336 (32)	

Hazard Ratio (95% CI)

0.5 1.0 2.0

Cooper NEJM 363:609 2010

IIIQ2b: In patients with renal failure (eGFR <45 mL/min/1.73m^2 or on dialysis) and diabetes should we prescribe Beta Blockers to prevent sudden cardiac death

- **Recommendations**
- In patients with diabetes and advanced CKD we suggest to at least try to install a selective B-blocking agent unless there is clear intolerance.

IIIQ3a: In patients with renal failure (eGFR <45 mL/min/1.73m^2 or on dialysis) and diabetes, should we prescribe lipid lowering therapy in primary prevention?

Recommendations

- We recommend to start lipid lowering therapy in diabetic patients with advanced CKD stage 3b and 4
- We suggest lipid lowering therapy can be considered in diabetic patients with advanced CKD stage 5
- We recommend lipid lowering therapy be stopped in diabetic patients on renal replacement therapy
- There is insufficient evidence to support one lipid lowering strategy over the other

IIIQ4a Should we recommend interventions aimed at increasing energy expenditure and physical activity in patients with renal failure (eGFR <45 mL/min/1.73m² or on dialysis) and diabetes?

IIIQ4b Should we recommend interventions aimed at reducing energy intake in patients with renal failure (eGFR <45 mL/min/1.73m² or on dialysis) and diabetes?

Recommendations

- We suggest diabetic patients with advanced CKD to perform physical exercise to reduce fat mass and improve QoL.
- There is no evidence of harm when promoting increased physical exercise
- When promoting weight loss in diabetic patients with weight loss, we recommend to supervise this process by a dietician and make sure that only fat mass is lost and malnutrition is avoided

IIIQ6: Should antiplatelet therapy be recommended in patients with renal failure (eGFR <45 mL/min/1.73m^2 or on dialysis) and diabetes, regardless of their cardiovascular risk?

Recommendations

- We do not recommend/recommend against adding Glycoprotein IIb/IIIa inhibitors or clopidogrel to standard care to reduce death, myocardial infarction, or need for coronary revascularization in persons with CKD and acute coronary syndromes or high-risk coronary artery intervention.
- We suggest starting aspirin in secondary prevention, unless there is a contra-indication or side-effects

IVQ1: Is there a contra-indication for systemic anticoagulative/platelet inhibiting strategies in patients with diabetic retinopathy and on hemodialysis?

- **Recommendations**
- We recommend to have an ophtalmologic evaluation, and if needed laser therapy, in diabetic patients with advanced CKD before starting anticoagulation
- We recommend regular ophtalmological follow up, and if needed laser therapy, in diabetics with advanced CKD who need anticoagulation

IQ6: Access to transplantation: What is the current access to the waiting list for dialysis patients with diabetes mellitus compared to patients without diabetes?

- Under review
- **Why this question?**

  The GDG wants to provide a recommendation on whether kidney transplantation is a viable option in diabetics, and whether some subgroups or some types of transplantation might be preferred. The answer to this question is however hampered by the fact that only observational data are available. However, selection bias might potentially blur the interpretation of what we find in the literature. As such, having an idea in how the take-on is of diabetics on transplantation might be important in the later interpretation of the observational data. This analysis, together with the analysis of the outcome of transplantation, can help us to formulate an advise whether we should stimulate transplantation in diabetics more, or rather refrain from doing so.

IIIQ1: In patients with renal failure (eGFR <45 mL/min/1.73m^2) and diabetes and coronary artery disease, is PCI or CABG or conservative treatment to be preferred?

- Under review
- **Why this question?**

  Chronic kidney disease and diabetes are two of the most important risk factors for poor outcomes in patients with coronary artery disease (CAD), but it is unknown whether CKD influences the efficacy of alternative CAD treatment strategies. PCI or CABG therapy may improve the major outcomes and survival but it increases the risk of specific complications, such as bleeding or infections. The question investigates whether maintaining conservative medical therapy or promoting potentially aggressive interventions (either PCI or CABG) would help to improve survival.

IIIQ2a: In patients with renal failure (eGFR <45 mL/min/1.73m^2 or on dialysis) and diabetes and with a cardial indication (heart failure, ischemic heart disease, hypertension) should we prescribe inhibitors of the RAAS system or aldosteron-antagonists as cardiovascular prevention?

- Under review
- **Why this question?**
- CKD patients III to V die more frequently than survive with progression to ESRD. Diabetes is a multiplier of CDV risk. Therefore in this particular population drugs that would slow progression and at the same time would be cardioprotective appear as a theoretical “first-line” therapy. Blockers of the RAA system are both renoprotective and cardioprotective in the general population. However in diabetics with advanced CKD, this potential benefit may be counterbalanced by the need to start dialysis or hyperkalaemia. As many patients will already be on these drugs before they develop advanced CKD, the question should also be asked whether withdrawing this drugs is justified.

IVQ1: What is the best way to treat polyneuropathy in patients with diabetes and renal failure (eGFR <45 mL/min/1.73m^2) or on dialysis?

- Under review
- **Why this question?**
- In diabetic CKD population the risk of neuropathy is increased. Diabetic peripheral neuropathy is associated with high morbidity, poor quality of life, and high risk of lower-extremity amputation. However, medication for patients with stages 4-5 CKD or on dialysis therapy, often needs to be adjusted, and side-effect profiles can be distinct and severe. This question addresses potentially therapeutically options for polyneuropathy and investigates benefits and risks associated with different medications.

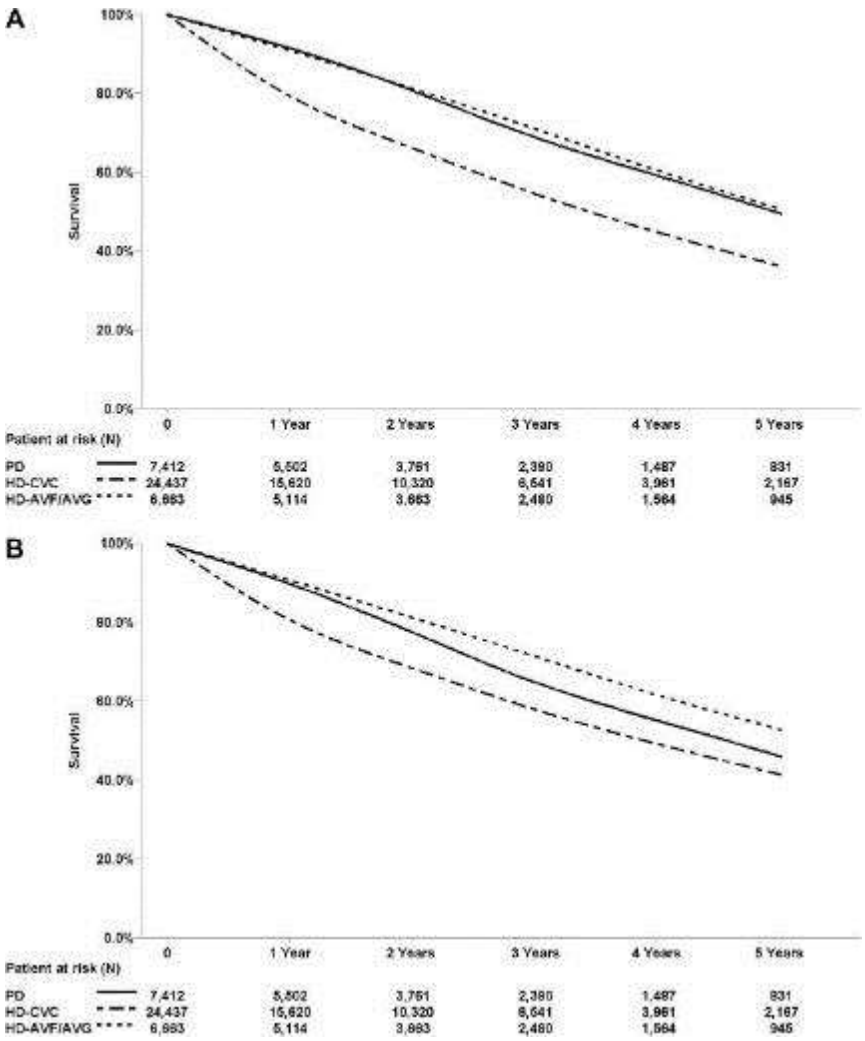
QIV: Vascular access: In patients with CKD stage 5 and diabetes mellitus, should a native fistula, a graft or a tunnelled catheter be preferred as initial access?

- We recommend reasonable effort is done to avoid tunneled catheters as access in diabetic patients starting dialysis as renal replacement therapy (1C)

(Very little PICO evidence)

Dialysis Access and Survival

PD
HD Fistula
HD Catheter



Unadjusted

Adjusted

Perl J et al. JASN 2011;22:1113-1121

IQVII Access to transplantation: : What is the benefit of renal transplantation for dialysis patients with diabetes mellitus?

- Under review
- **Why this question?**

  Diabetic CKD patients mostly have complex comorbidity; Posttransplantation medication can deteriorate their glycemic control and worsen their already compromised vascular bed. Therefore, we need to ascertain whether diabetic patients may take advantage of kidney transplantation, in terms of major outcomes. To this end, it is also important to elucidate whether a specific type of transplantation (e.g. kidney-pancreas vs kidney alone; living donor vs cadaveric..) should be preferred.

Transplantation Survival vs. Waiting List

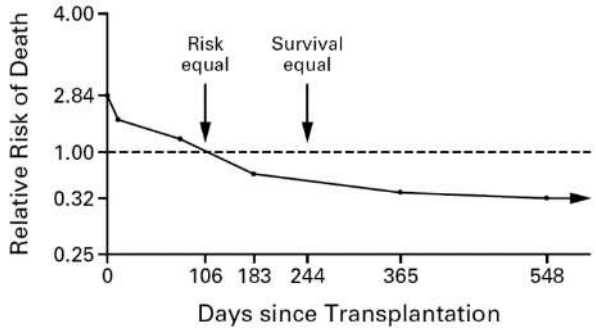


Figure 2. Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

TABLE 3. OUTCOME AMONG RECIPIENTS OF FIRST CADAVERIC TRANSPLANTS, ACCORDING TO CHARACTERISTICS AT THE TIME OF INITIAL PLACEMENT ON THE WAITING LIST, 1991–1997.*

GROUP	RELATIVE RISK 18 MO AFTER TRANSPLANTATION (95% CI)†	P VALUE	TIME AT WHICH RISK OF DEATH EQUALS THAT IN REFERENCE GROUP	TIME AT WHICH LIKELIHOOD OF SURVIVAL EQUALS THAT IN REFERENCE GROUP	PROJECTED YEARS OF LIFE (IN REFERENCE GROUP) WITHOUT TRANSPLANTATION†‡	PROJECTED YEARS OF LIFE WITH TRANSPLANTATION‡
			days after transplantation			
All recipients of first cadaveric transplants	0.32 (0.30–0.35)	<0.001	106	244	10	20
Age						
0–19 yr	0.33 (0.12–0.87)	0.03	3	5	26	39
20–39 yr	0.24 (0.20–0.29)	<0.001	11	57	14	31
40–59 yr	0.33 (0.29–0.37)	<0.001	95	251	11	22
60–74 yr	0.39 (0.33–0.47)	<0.001	148	369	6	10
Sex						
Male	0.34 (0.30–0.38)	<0.001	110	255	10	19
Female	0.30 (0.26–0.34)	<0.001	94	220	11	23
Race						
Native American	0.50 (0.27–0.96)	0.04	123	304	9	14
Asian	0.43 (0.25–0.75)	0.003	161	673	15	23
Black	0.52 (0.44–0.62)	<0.001	109	305	13	19
White	0.28 (0.25–0.30)	<0.001	100	220	9	19
Cause of end-stage renal disease						
Diabetes	0.27 (0.24–0.30)	<0.001	57	146	8	19
Glomerulonephritis	0.39 (0.31–0.48)	<0.001	130	360	11	18
Other	0.38 (0.33–0.43)	<0.001	137	353	12	20
Age and diabetes status						
20–39 yr, no diabetes	0.38 (0.28–0.50)	<0.001	14	220	20	31
20–39 yr, diabetes	0.18 (0.14–0.23)	<0.001	10	35	8	25
40–59 yr, no diabetes	0.38 (0.33–0.43)	<0.001	126	356	12	19
40–59 yr, diabetes	0.27 (0.23–0.32)	<0.001	66	181	8	22
60–74 yr, no diabetes	0.37 (0.30–0.46)	<0.001	159	442	7	12
60–74 yr, diabetes	0.46 (0.34–0.61)	<0.001	89	247	5	8

Wolfe NEJM 341:1725 1999

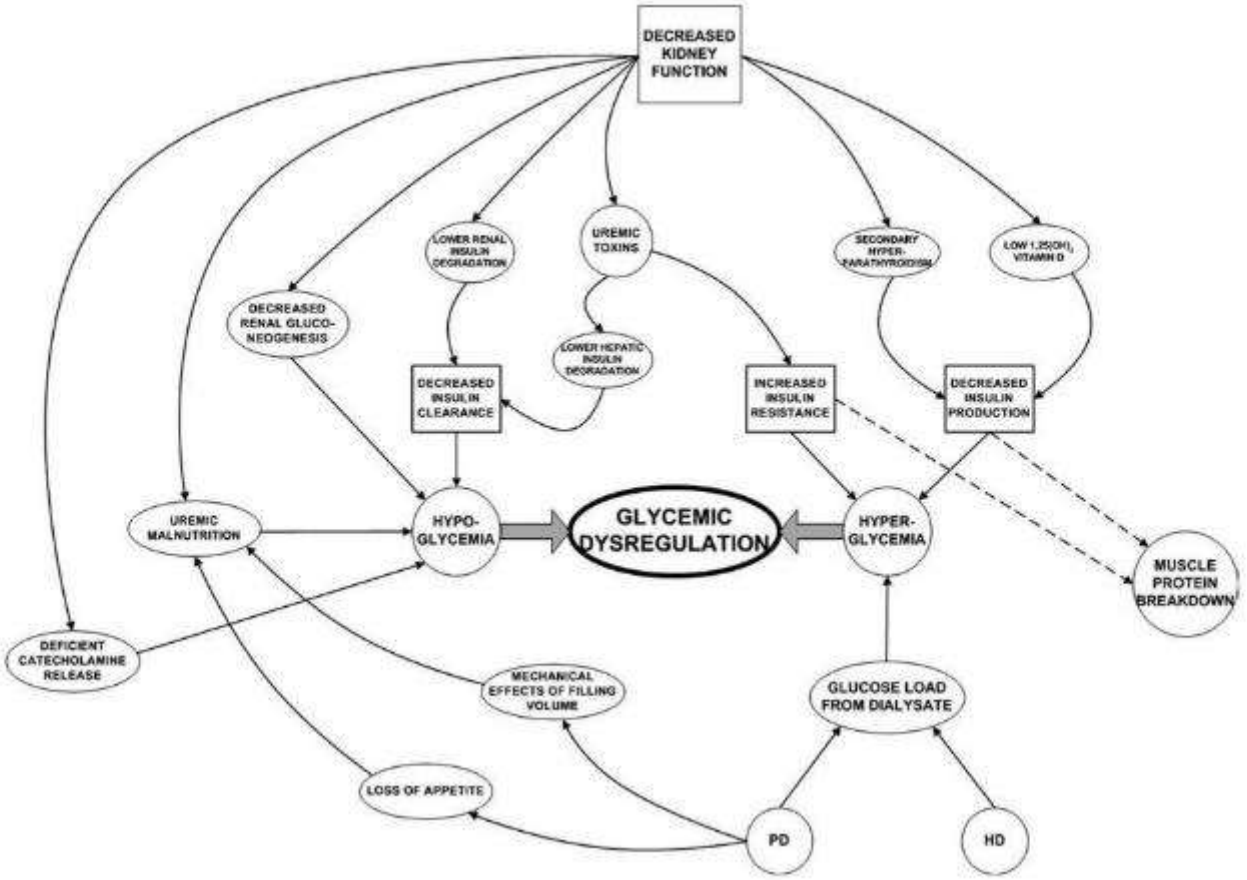
Insulin & the Kidney

- Endogenous insulin primarily degraded by liver, exogenous by kidney
- Freely filtered by glomerulus
- Reabsorbed in proximal tubule and degraded
- Uptake & degradation in peritubular endothelium → Clearance >GFR
- Peritubular degradation ↑ in CKD, maintains insulin cleareance
- GFR<20 ml/min → Insulin requirements↓

After Dialysis Initiation:

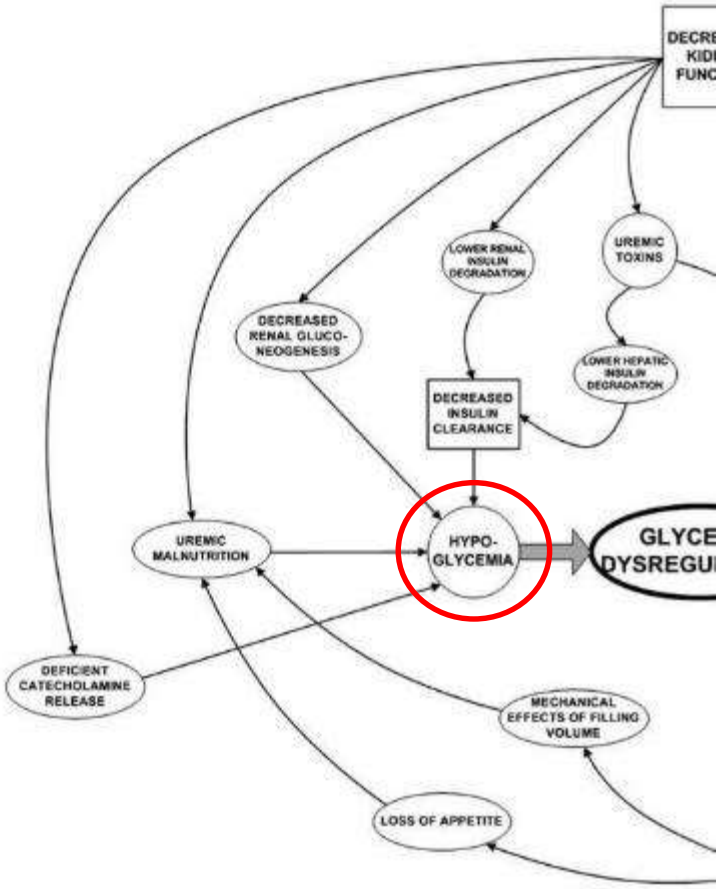
- Insulin resistance ↓
- Food intake ↑
- Glucose administration ↑ (PD)

CKD and Glycaemic Control



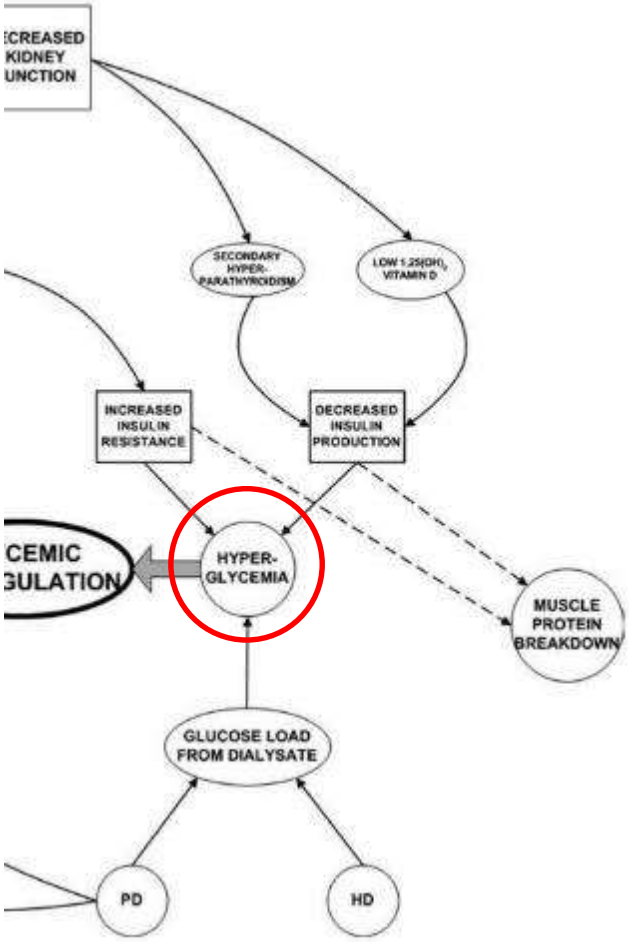
Kovesdy AJKD 52:766 2008

CKD and Glycaemic Control



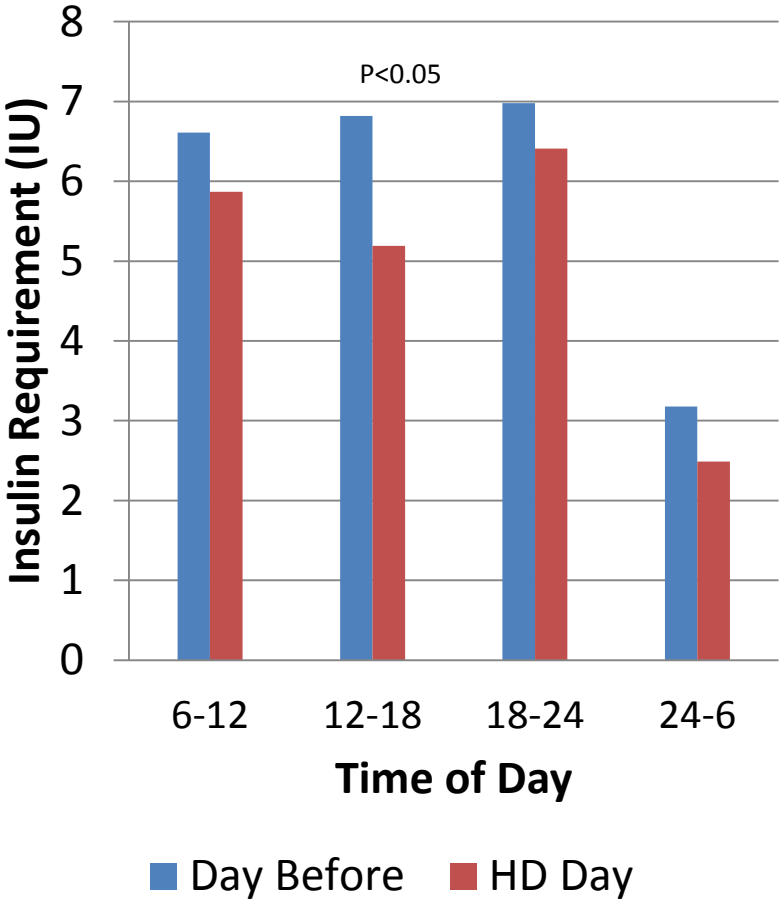
Kovesdy AJKD 52:766 2008

CKD and Glycaemic Control



Kovesdy AJKD 52:766 2008

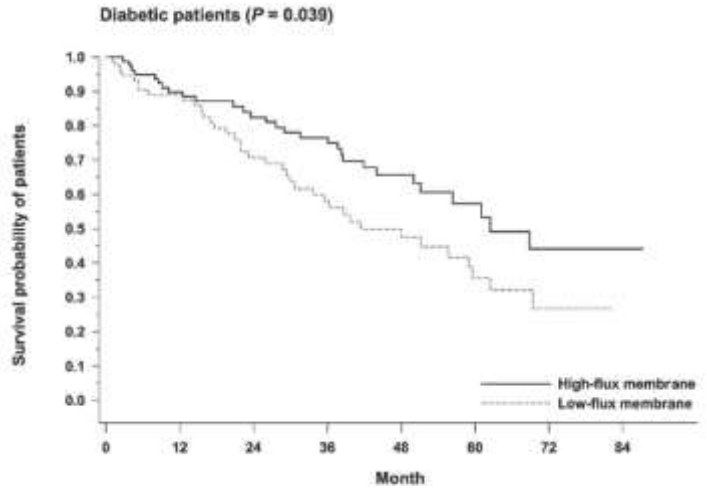
HD reduces Insulin Requirements

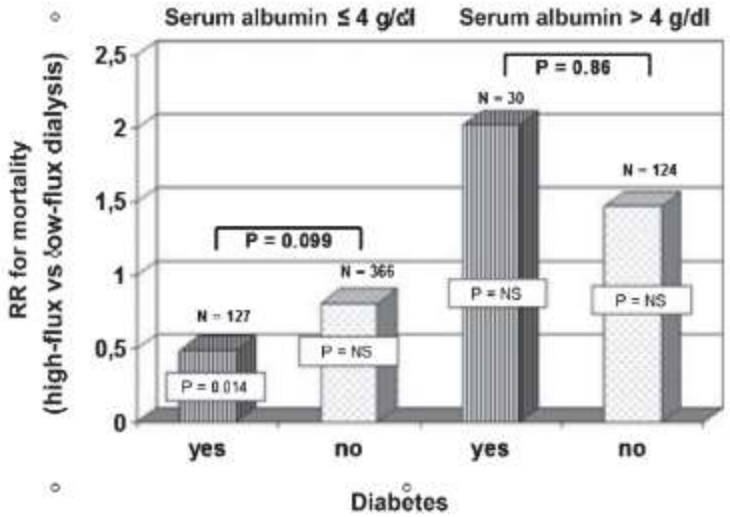


- 10 T2DM HD pts.
- Euglycaemic clamp 0.3 IU/hr + 3 IU bolus before every meal
- Bolus: no difference
- Basal insulin 0.4 IU/hr pre-HD vs. 0.3 post-HD (p=0.01)

Sobngwi Diab Care 33:1409 2010

High-Flux HD good for Malnourished Diabetic Patients?





The MPO Study

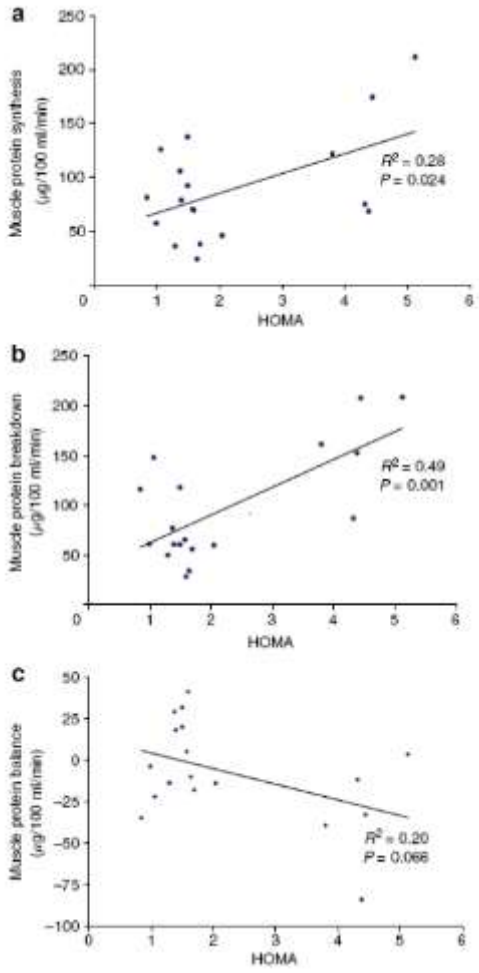
738 incident HD patients
RCT High-flux vs. Low-flux

157 DM pts. (T1DM 12%)

Adjusted Hazard Rate 0.62

Locatelli JASN 20:645 2009

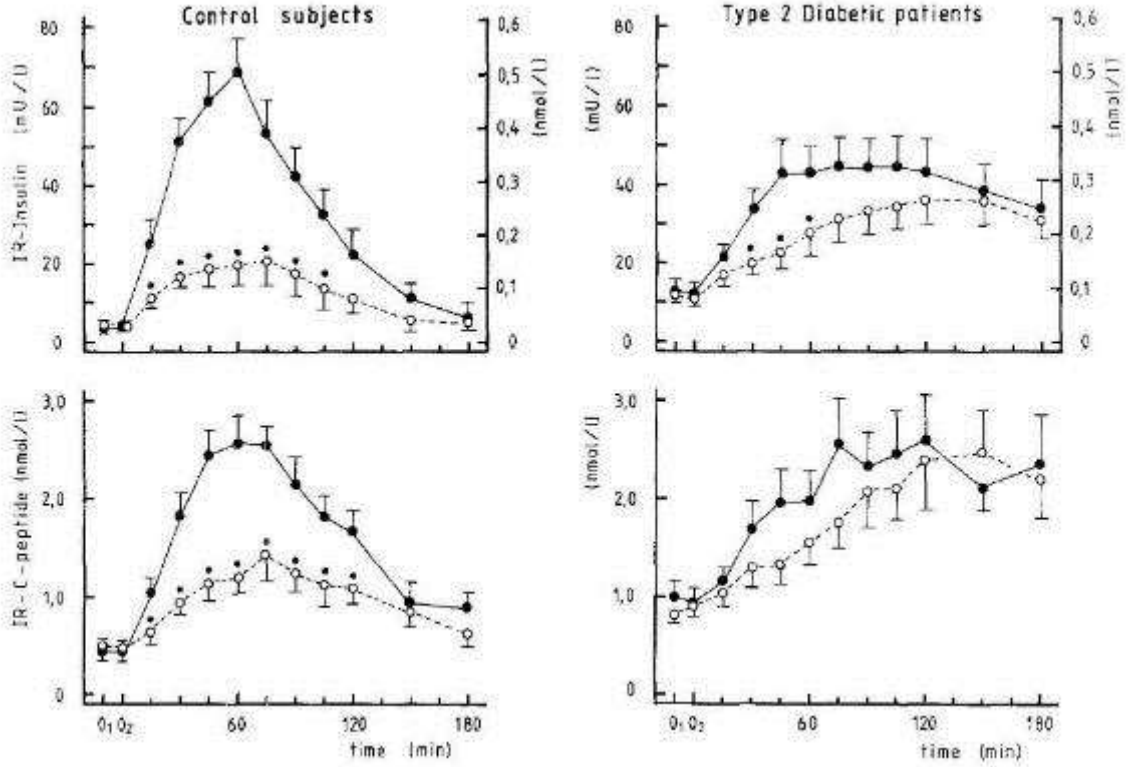
Insulin resistance associated with PEW in non-diabetic HD patients



- 18 Non-diabetic HD patients
- HOMA correlated to BMI ($r=0.54$, $p=0.02$)
- After adjusting for CRP only breakdown significantly correlated ($p<0.01$)

Siew KI 71:146 2007

The incretin effect



●: Oral glucose load
○: Isoglycaemic
IV glucose infusion

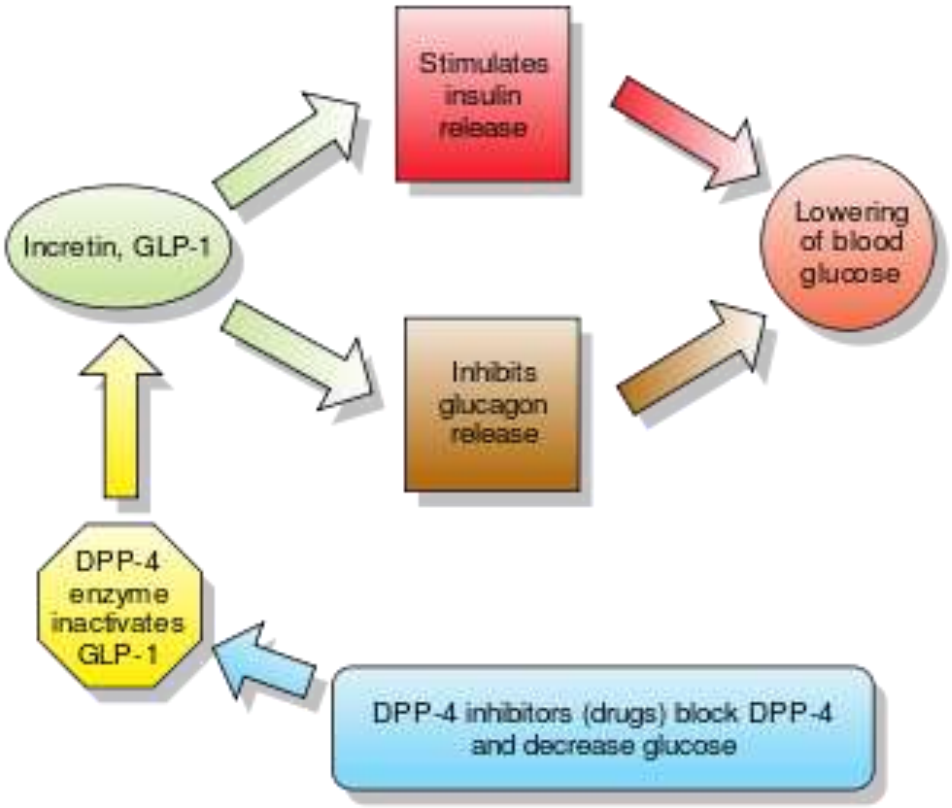
Nauck Diabetologia 29,46 1986

The Incretins

- Hormones
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic peptide (GIP)
- Stimulate insulin release
- Inhibit glucagon release
- Gastrointestinal-mediated glucose disposal. Oral vs. Isoglycaemic IV glucose infusion) (GIGD)
- Secreted from intestinal endocrine mucosal cells in response to food intake
- Normals: 70% of insulin response after food intake

  T2DM: 0-30%

Incretins

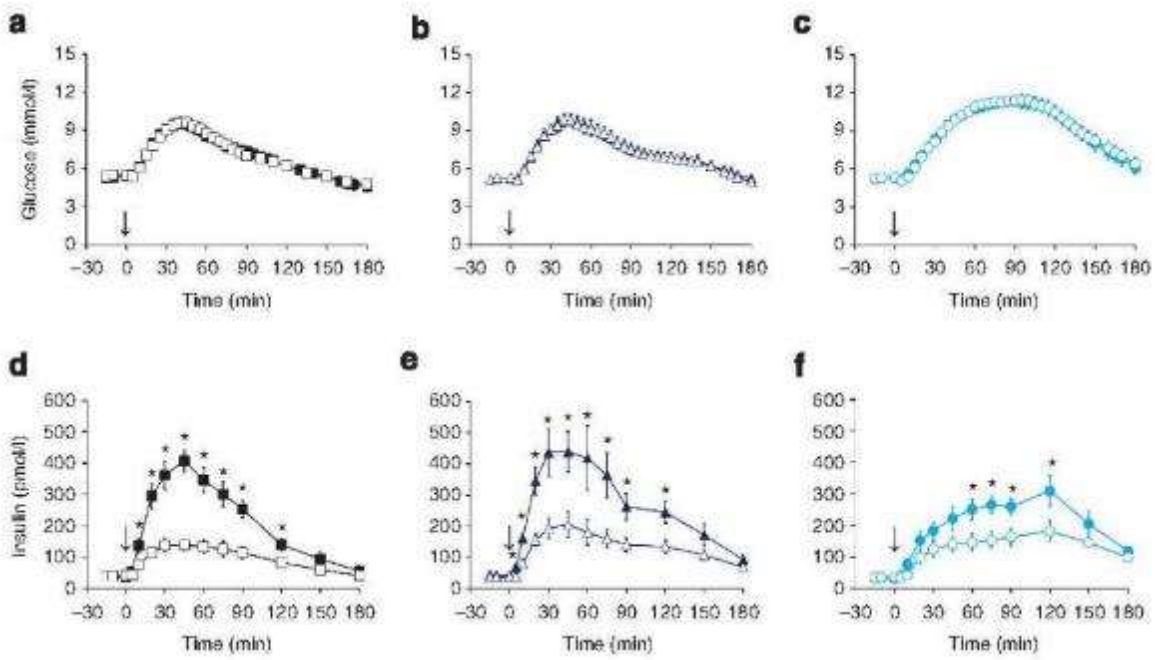

Stimulates insulin release
Incretin, GLP-1
Lowering of blood glucose
Inhibits glucagon release
DPP-4 enzyme inactivates GLP-1
DPP-4 inhibitors (drugs) block DPP-4 and decrease glucose

Incretins in NonDM ESRD

	Controls	ESRD Normal Glucose Tolerance	ESRD Impaired Glucose Intolerance
No. Patients	11	10	10
HOMA-IR	1.33	1.11	1.47
Glucose Rx IIGT (g)	31	46*	52*

Isoglycaemic
IV glucose infusion

Filled: Oral
Open: IV



Idorn KI 2013; 83:915

GLP-1 and GIP

Normal | ESRD Normal OGT | ESRD Impaired OGT

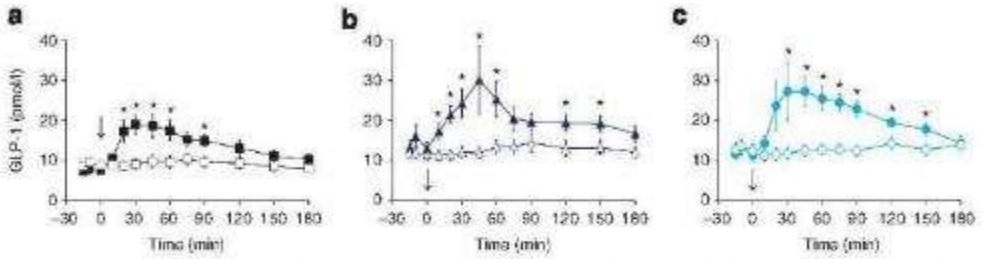


Figure 4 | Total glucagon-like peptide-1 (GLP-1). Plasma total GLP-1 responses during oral glucose tolerance test (filled symbols) and isoglycemic intravenous glucose infusion (open symbols) in healthy control subjects (**a**) and in patients with end-stage renal disease and normal glucose tolerance (**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.

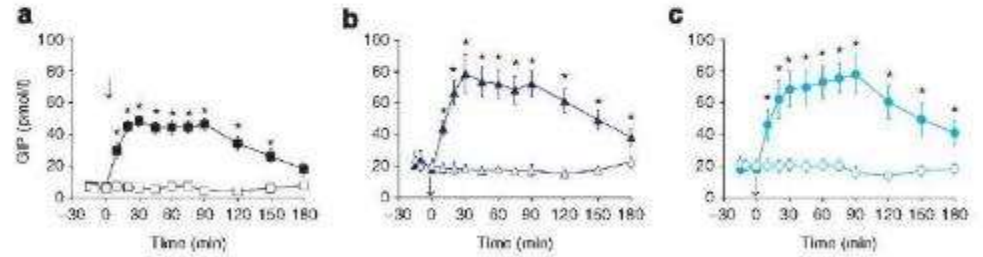


Figure 5 | Total glucose-dependent insulinotropic polypeptide (GIP). Plasma total GIP responses during oral glucose tolerance test (filled symbols) and isoglycemic intravenous glucose infusion (open symbols) in healthy control subjects (**a**) and in patients with end-stage renal disease and normal glucose 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

Glucagon

Normal | ESRD Normal OGT | ESRD Impaired OGT

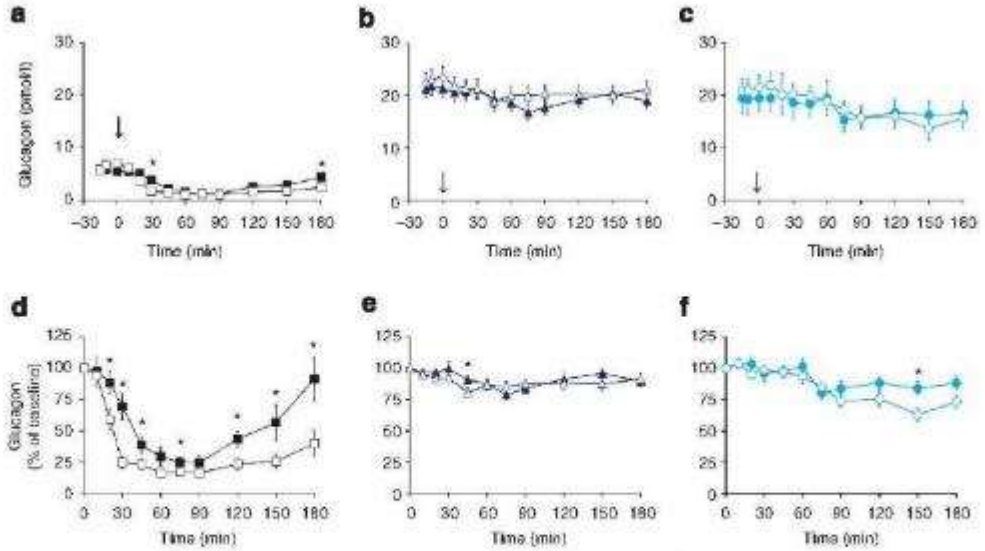
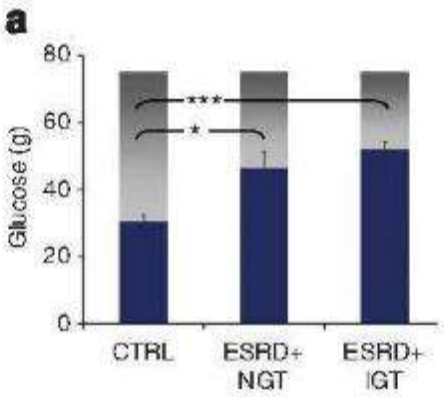
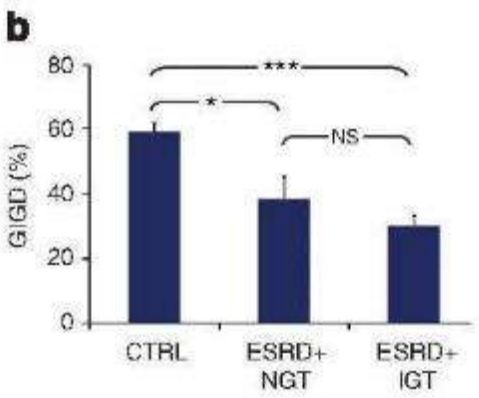


Figure 6 | Glucagon. Glucagon responses during oral glucose tolerance test (filled symbols) and isoglycemic intravenous glucose infusion (open symbols) in control subjects (**a** and **d**) and in patients with end-stage renal disease and normal glucose tolerance (**b** and **e**) or impaired glucose 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.

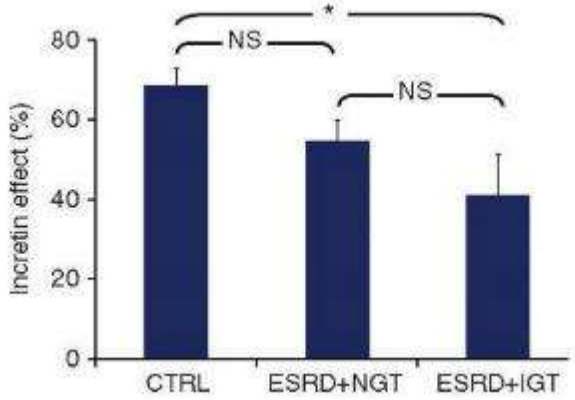
Idorn KI 2013; 83:915

G-I mediated Glucose Disposal and Incretin Effect





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



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 (as in T2DM)
- Peripheral insulin resistance
- Fasting hyperinsulinaemia

HgbA1C

IIQ1 In patients with renal failure(eGFR <45 mL/min/1.73m^2) or on dialysis, and diabetes mellitus should we aim to lower HbA1C by more tight glycaemic control

- We recommend against more tight glycaemic control if this results in or increases the risk for hypoglycemic episodes (**1A**)
- We recommend cautious tightening of the glycaemic control to lower HbA1C when values are >8.5% (70 nnol/mol)(**1C**)
- We suggest cautious tightening of glycaemic control when HbA1C values are >7% (53 mmol/mol) but <8.5% (70 mmol/mol) only when the projected benefits (microvascular complications, retinopathy) clearly outweigh the risk for hypoglycaemia, taking into account general condition of the patient (**2D**)

ERBP Guidelines: in preparation

IFCC HbA1c Units

- IFCC (mmol/mol) = [HbA1c (%) -2.15] x 10.93
- HbA1c (%) = [IFCC +23.5]/10.93

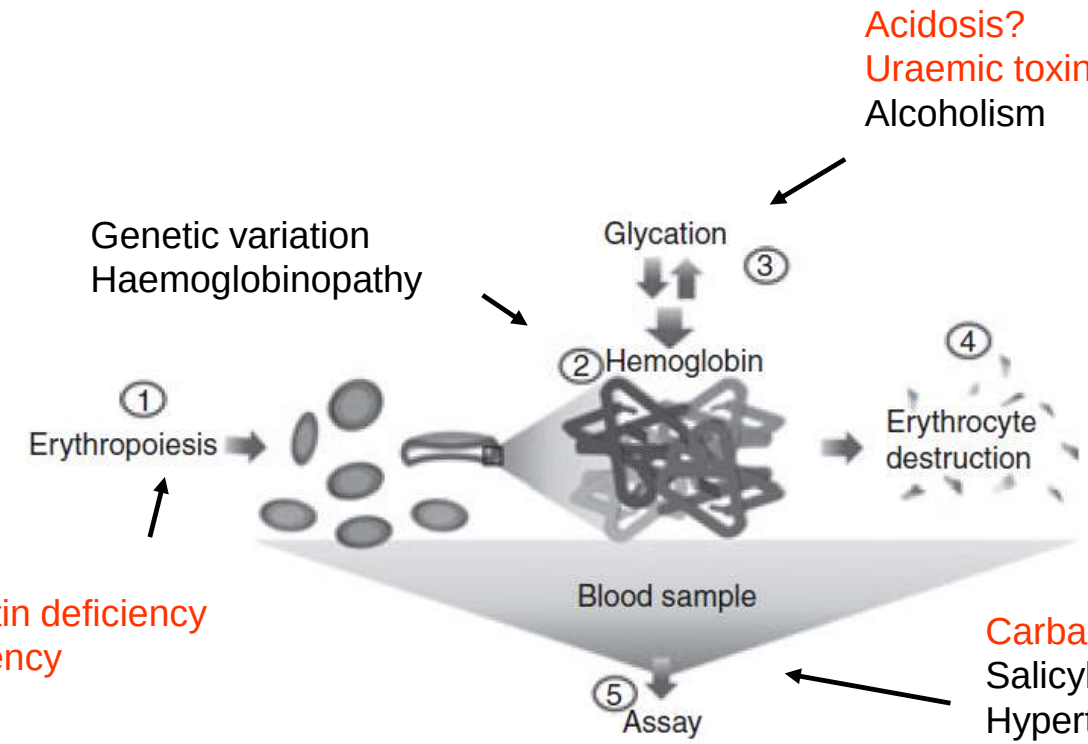
- IFCC→HbA1c(%): add 24 and divide by 11
- HbA1c(%)→IFCC: multiply by 11 and subtract 24

DCCT HbA1c (%)	IFCC HbA1c (mmol/l)	Average blood glucose
6	42	7.0
7	53	8.6
8	64	10.1
9	75	11.7

Several Sources of Error

- HbA_{1c} is 'falsely' too low with reduced erythrocyte survival

(younger erythrocyte cohort – shorter exposure)

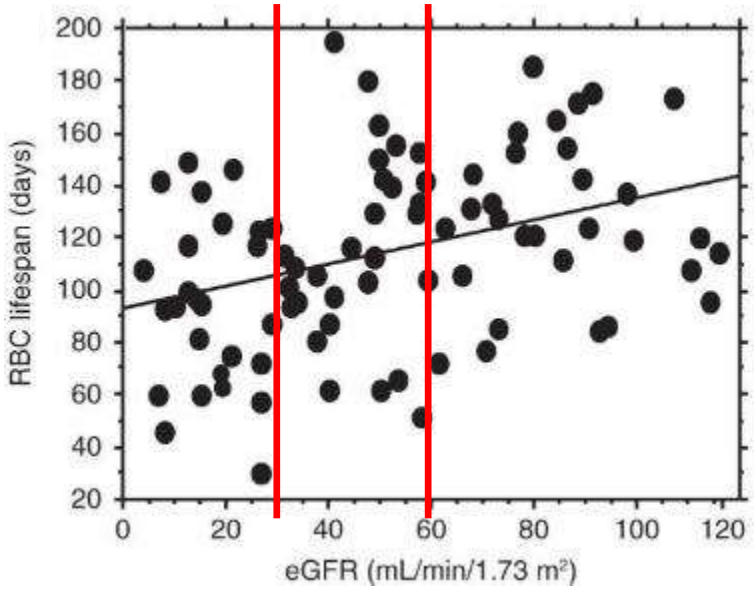


Modified from Gallagher et al. J Diabetes 2009

With thanks to Rikke Borg

Significant correlation between RBC lifespan og eGFR

- 86 diabetic pts. with renal dysfunction not on dialysis
- Mean RBC lifespan [eGFR <30 ml/min] 95 ± 30 days
  [eGFR >60 ml/min] 127 ± 30 days

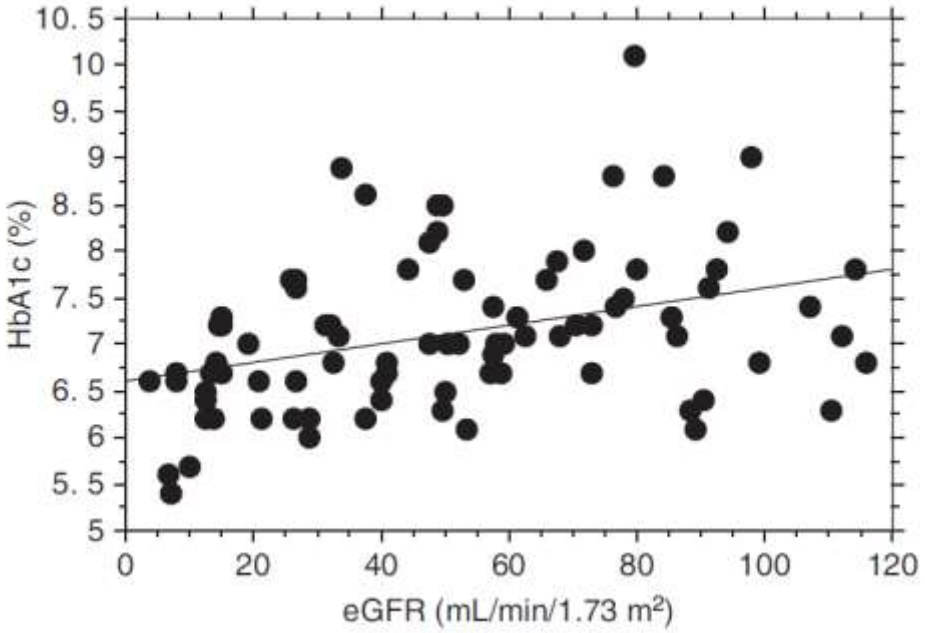


K. Shima; Ann Clin Biochem; 2012, vol. 49, 68-74

With thanks to Rikke Borg

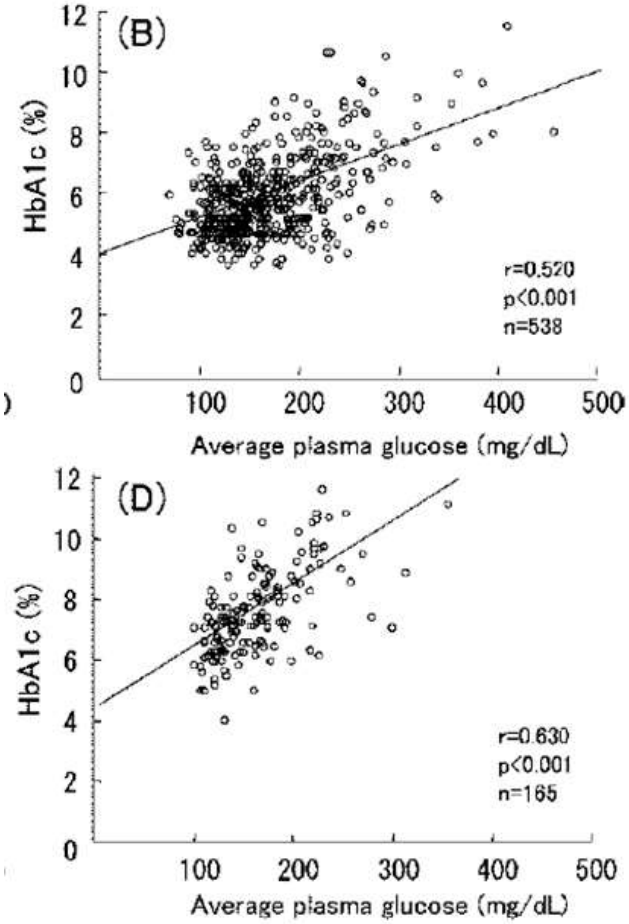
HbA1c is significantly correlated to eGFR

- 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



With thanks to Rikke Borg

HbA1c in HD patients



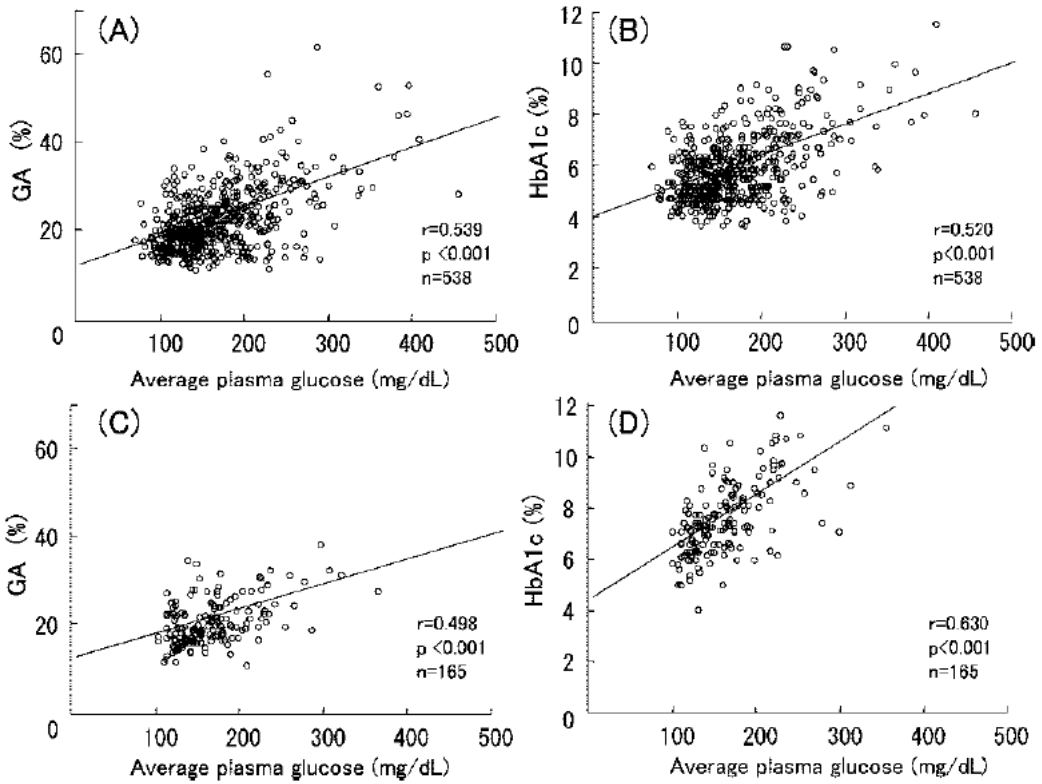
DM HD

DM Normal
Renal function

538 DM HD pts.
365 DM normal renal function

Inaba JASN 18:896 2007

Glycated Albumin vs. Hb A1C



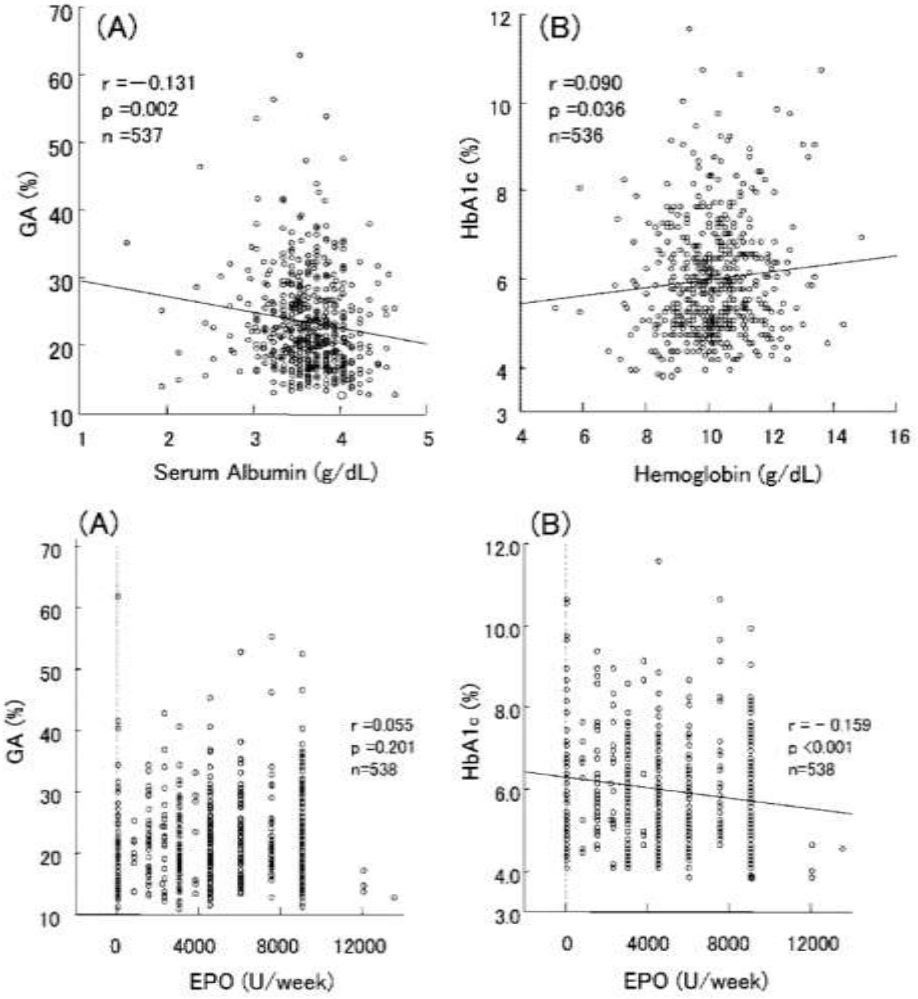
DM HD

DM Normal
Renal function

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

Inaba JASN 18:896 2007

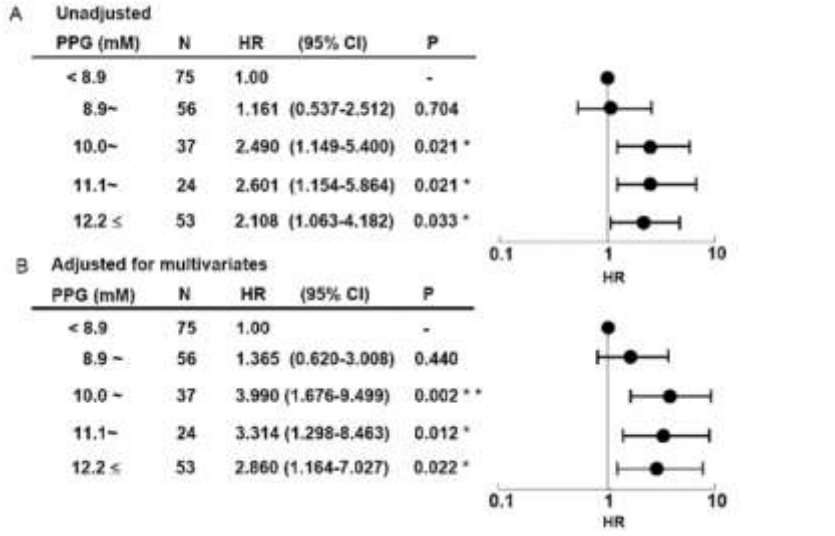
Hb, EPO & Hb A1C



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

Inaba JASN 18:896 2007

Post-prandial Glucose: The Truth?

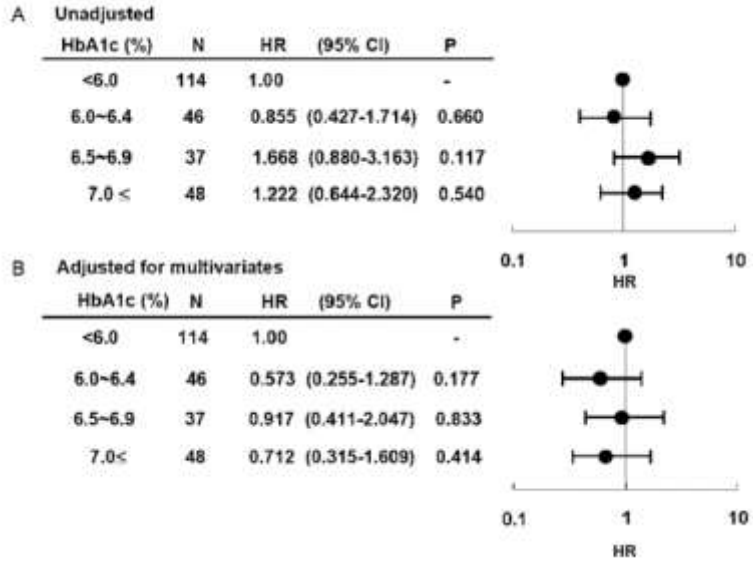


A Unadjusted

PPG (mM)	N	HR	(95% CI)	P
< 8.9	75	1.00		-
8.9~	56	1.161	(0.537-2.512)	0.704
10.0~	37	2.490	(1.149-5.400)	0.021 *
11.1~	24	2.601	(1.154-5.864)	0.021 *
12.2 ≤	53	2.108	(1.063-4.182)	0.033 *

B Adjusted for multivariates

PPG (mM)	N	HR	(95% CI)	P
< 8.9	75	1.00		-
8.9 ~	56	1.365	(0.620-3.008)	0.440
10.0 ~	37	3.990	(1.676-9.499)	0.002 * *
11.1~	24	3.314	(1.298-8.463)	0.012 *
12.2 ≤	53	2.860	(1.164-7.027)	0.022 *



A Unadjusted

HbA1c (%)	N	HR	(95% CI)	P
<6.0	114	1.00		-
6.0~6.4	46	0.855	(0.427-1.714)	0.660
6.5~6.9	37	1.668	(0.880-3.163)	0.117
7.0 ≤	48	1.222	(0.644-2.320)	0.540

B Adjusted for multivariates

HbA1c (%)	N	HR	(95% CI)	P
<6.0	114	1.00		-
6.0~6.4	46	0.573	(0.255-1.287)	0.177
6.5~6.9	37	0.917	(0.411-2.047)	0.833
7.0<	48	0.712	(0.315-1.609)	0.414

- 245 incident DM HD pts.
- 93% T2DM
- Followup 43 months (1-130)
- Mean postprandial blood glucose
- Adjusted RR for death $4.0^{p<0.002}$

Postprandial BG (mM)	<10	>10
No.	131	114
Diet alone	31%	9%
Phosphate (mM)	1.72	1.58*
Creatinine (µM)	700	640*
BMI (kg/m2)	22.3	21.3
Hb A1C (%)	5.5	6.2

Shima Nephrology 15:632 2010

HbA1c in PD

- 850 PD pts. with DM
- 4566 measurements

BG (mg/dL) = 24.1 + 28.6 x HbA1c (%) – 12.2 x albumin (g/dL)

Hoshino AJN 37:413 2013

Alternatives to HbA_{1c}?

- Other Markers: glycated proteins
  - Glycoalbumin
  - Fructosamine
- P-Glucose monitoring
  - 7-point profiles x 2-3/week before consultation
- Download from blood sugar devices
  - Most have software med statistical programs: Average BS, medians, variation (SD), 25-75% intervals

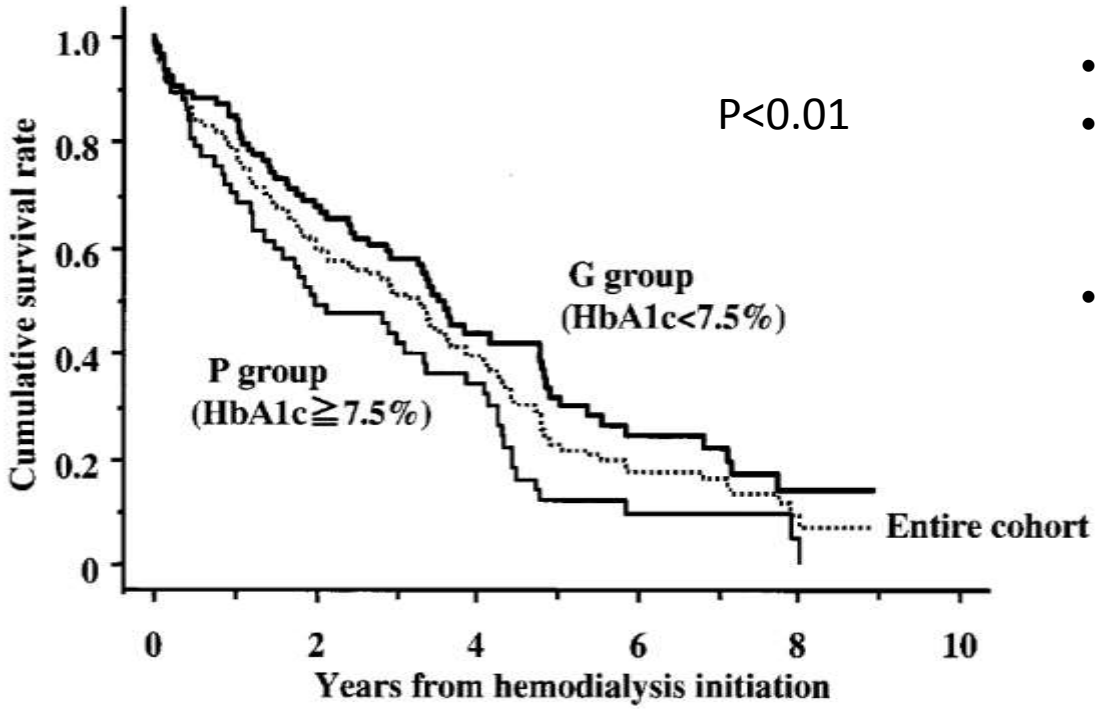
With thanks to Rikke Borg

Conclusion - HbA_{1c} in CKD

- Better than nothing?
  - High HbA_{1c} – disregulated hyperglycaemia
  - Low HbA_{1c} – possible anæmia?
  - Target HbA_{1c} < 7% - probably not relevant
- Be aware of sources of error
  - Investigate patient paraclinical situation
  - Is haematology stable?
    - Haemoglobin, iron, reticulocytes
    - Is Epo-dosis stable?
    - Estimation of blood loss
  - Monitor glucose concentrations
  - Do not use HbA_{1c} to diagnose diabetes

With thanks to Rikke Borg

Predialysis Glycaemic Control and ESRD Survival

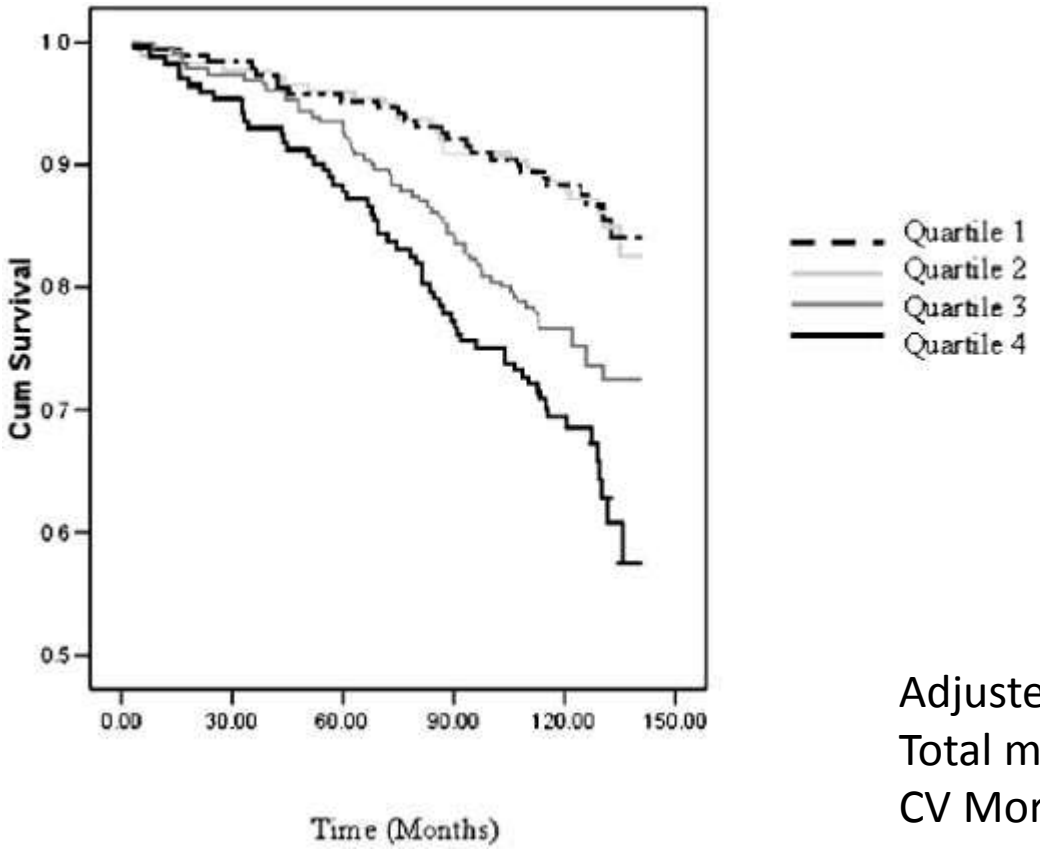


P<0.01

- 150 incident DM HD pts.
- Hb A1C at inclusion:
  - Good <7.5%
  - Poor ≥7.5%
- Adjusted HR 1.133 per 1% HbA1C increase

Morioka Diabetes Care 24:909 2001

Hgb A1C in Non-DM CKD



MDRD sudy
585 pts. eGFR 25-55
255 pts. eGFR 13-24
After exclusions (DM)
768 patients
Baseline Hgb A1C (%)

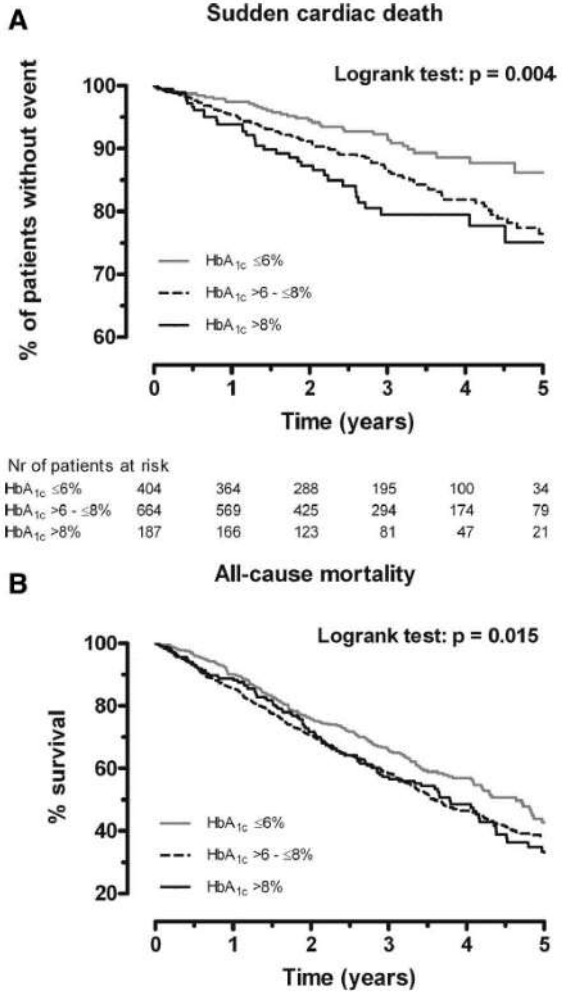
Q1	5.0
Q2	5.4
Q3	5.7
Q4	6.3

Adjusted Hazard Ratio (per % Hgb A1C)

Total mortality	1.73	p<0.001
CV Mortality	1.53	p=0.07

Menon CJASN 16:3411 2005

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

Fresenius Database

24,875 pts.
95% T2DM

T2DM

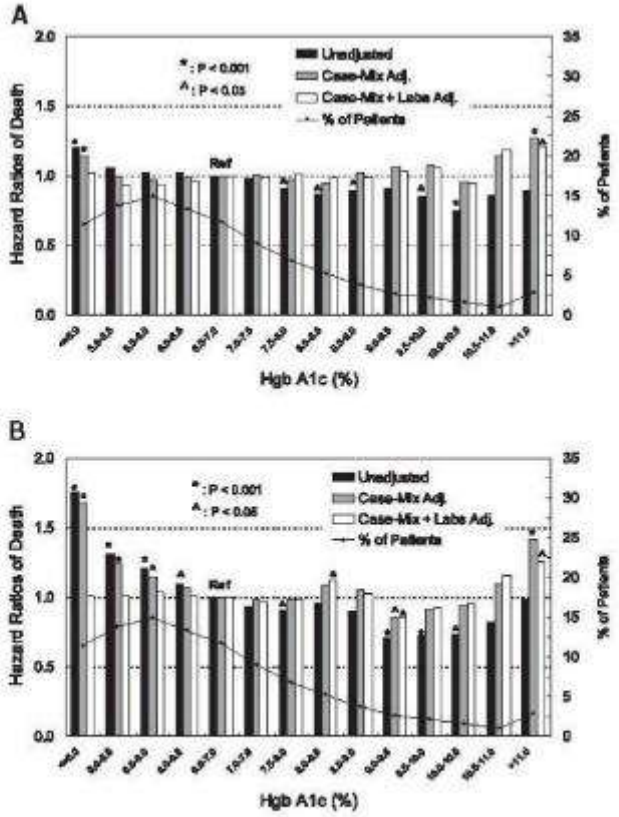


Figure 2. (A) Standard Cox models for mortality based on HgbA1c at baseline. (B) Time-dependent Cox models for mortality (laboratory results adjusted quarterly).

T1DM

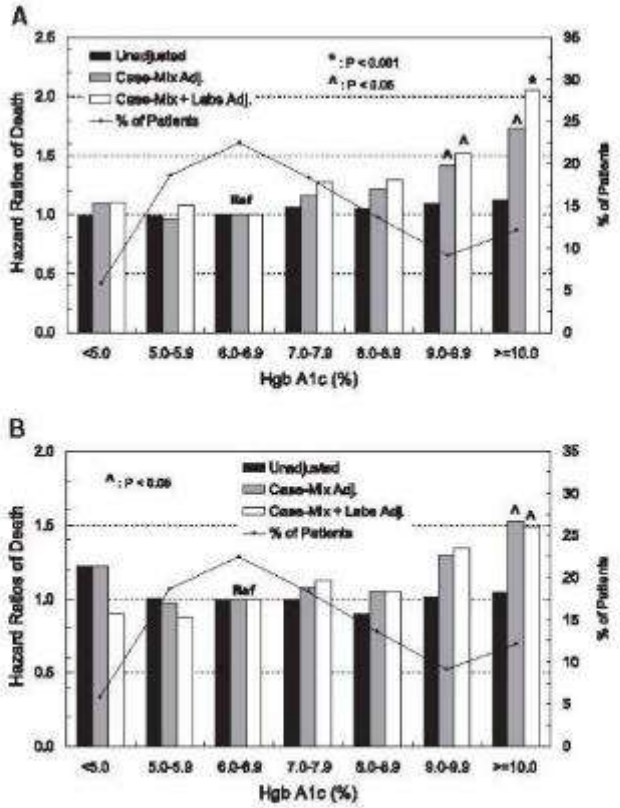


Figure 3. (A) Standard Cox models for patients with type 1 DM (n = 1367) only. (B) Time-dependent Cox model for patients with type 1 DM as above.

Baseline

Average

Williams CJASN 2010; 5:1595

Hgb A1C & HD Mortality

DaVita Database

Baseline

Average

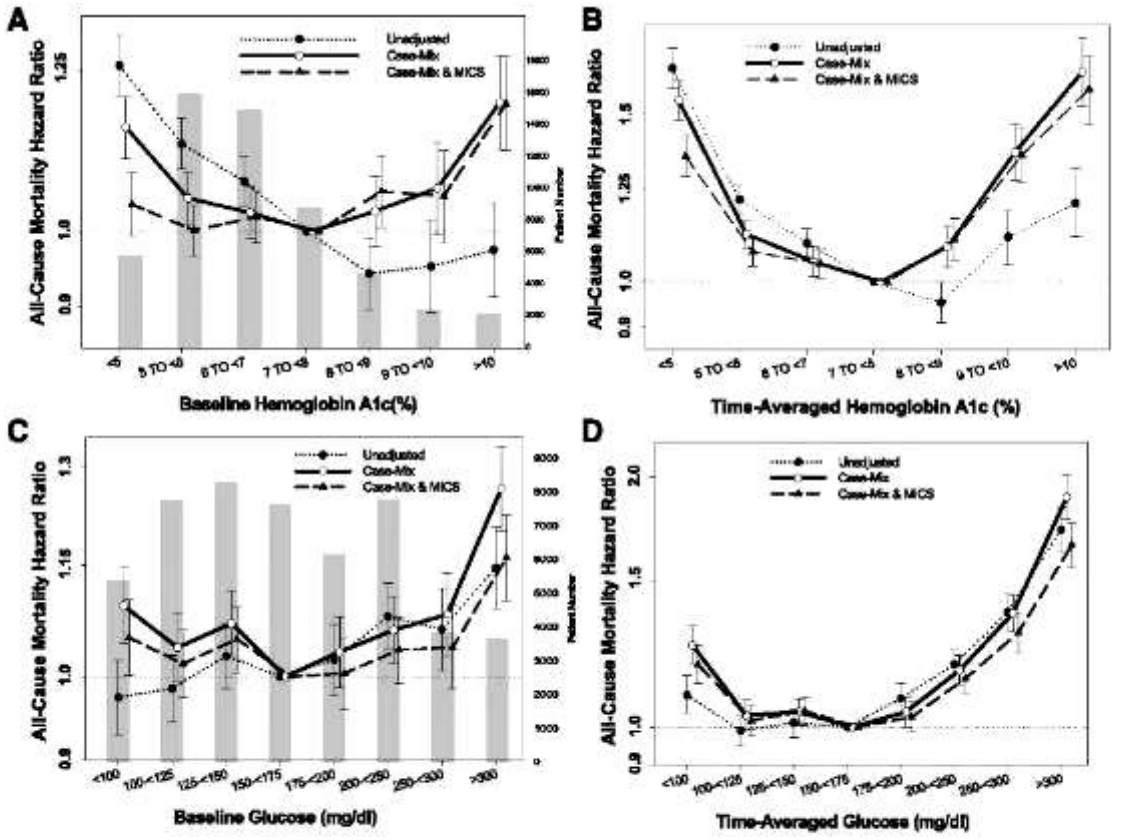


FIG. 1. HRs of all-cause mortality of the entire range of A1C in 54,757 MHD patients using standard Cox proportional hazards regression (*A*), a time-averaged model (*B*), and HRs of all-cause mortality of serum glucose in 50,383 diabetic MHD patients using standard Cox proportional hazards regression (*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.

96% T2DM

Hgb A1C

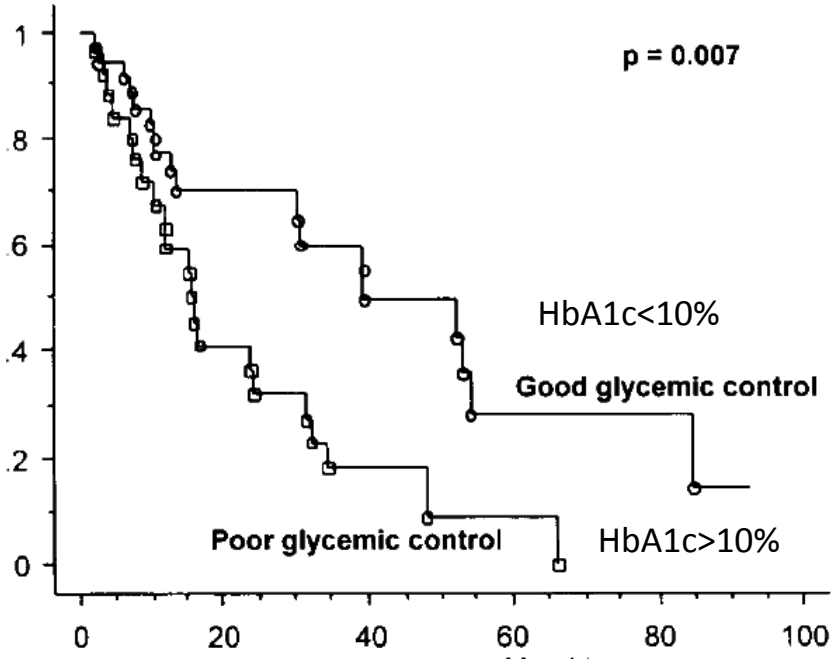
Random blood Glucose

(100 mg% = 5.5 mM)

Ricks Diabetes 2012; 61:708

Predialysis HbA1C predict survival on PD

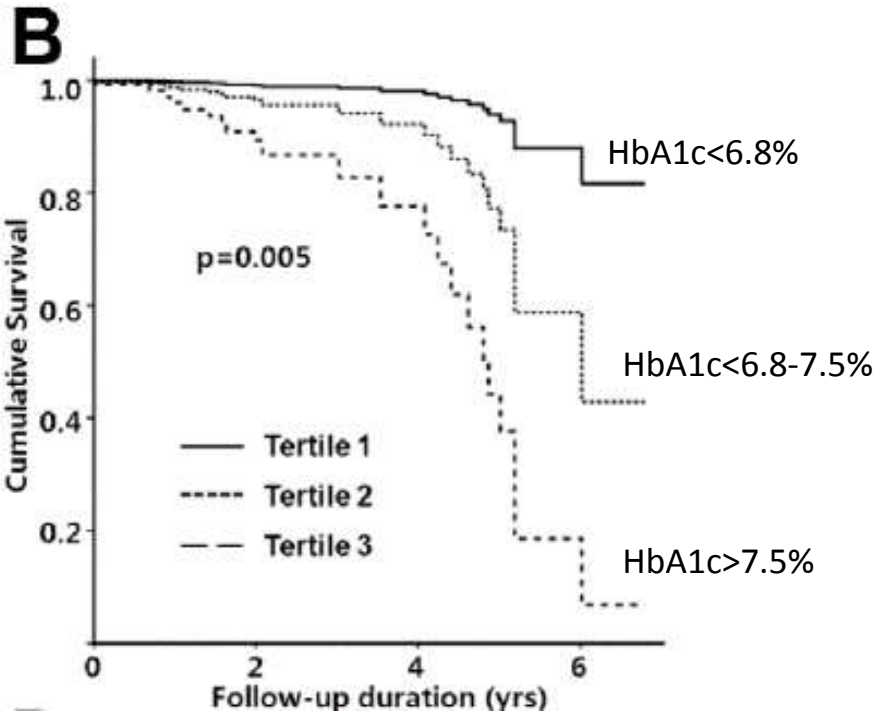
PD



60 patients

Yu PDI 17:262-68 1997

HD



Yoo PlosOne 7:e30072 2012

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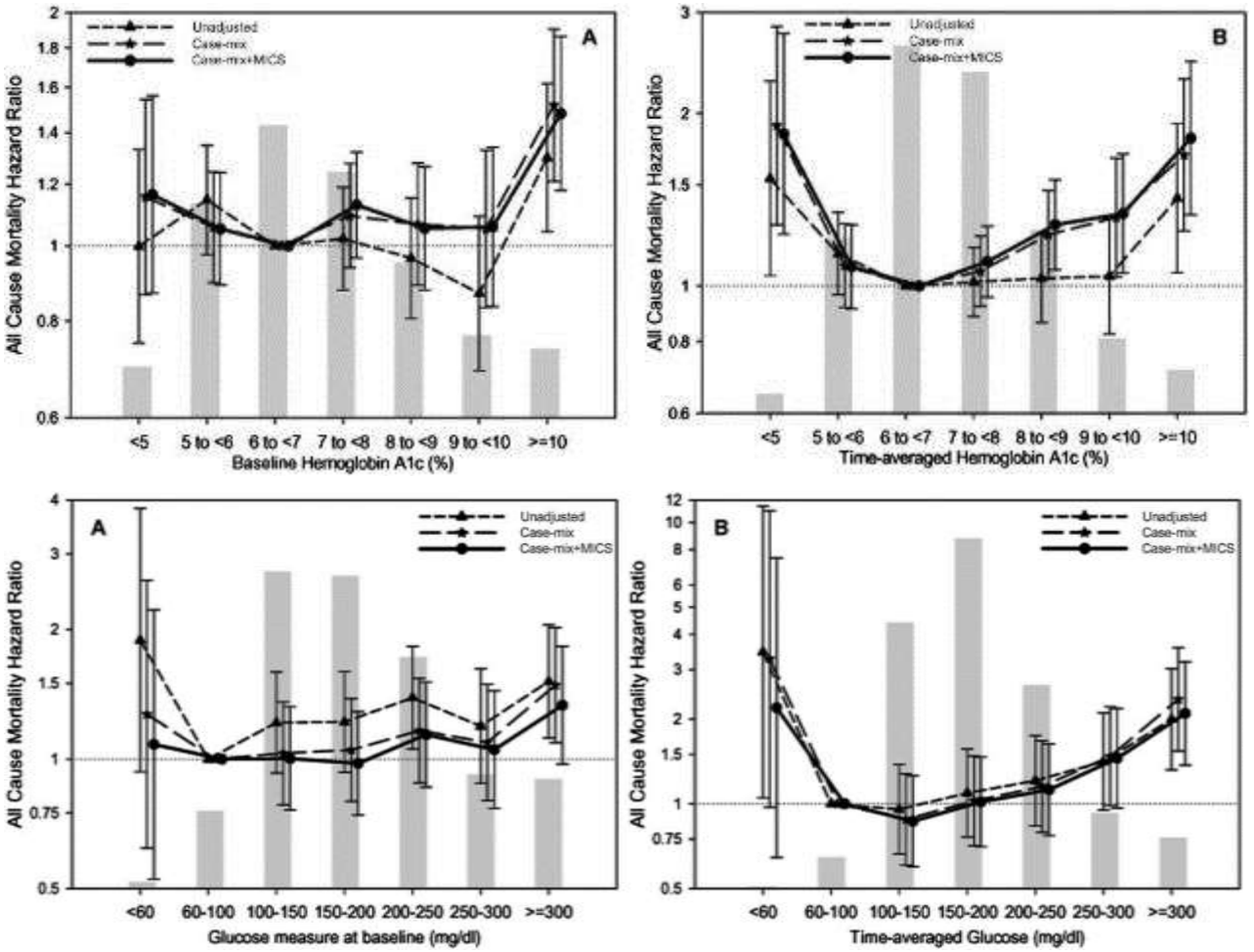


HgbA1C

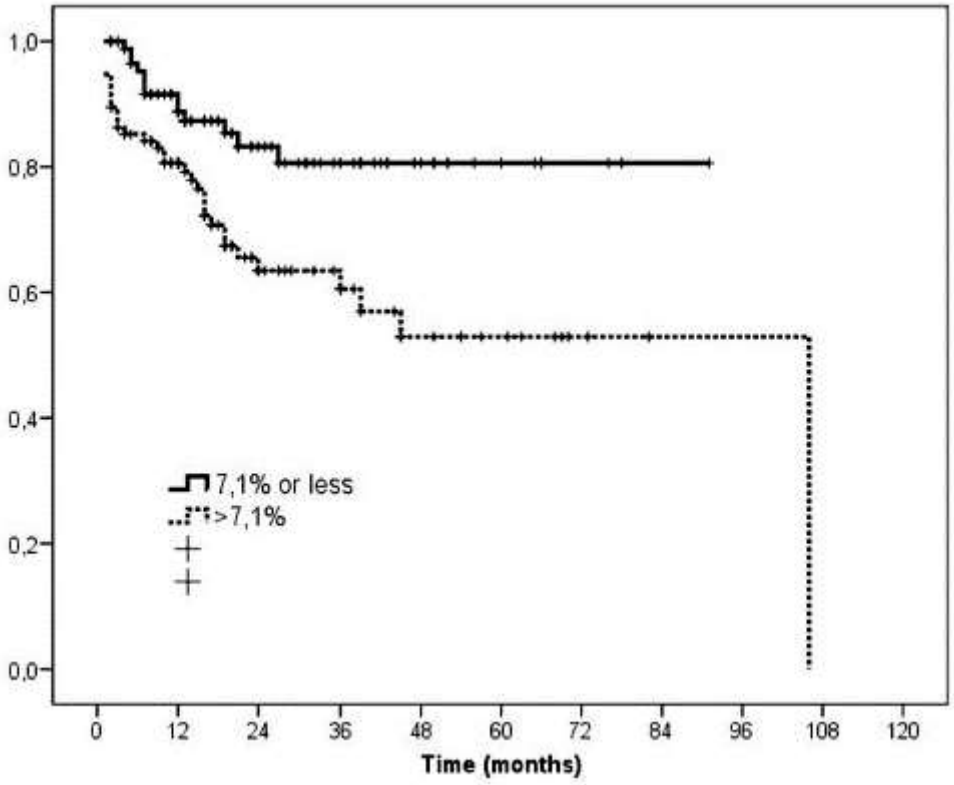
Random Blood glucose

2798 PD pts.

Duong CJASN 2011; 6:1041

Diabetic Control reduces Incidence of Exit Site Infections

- 183 incident PD patients
- Hb A1C at initiation <> 7.1%
- 0.23 vs. 0.12 episodes/yr (p<0.01)
- Adjusted hazard ration 2.65 (p<0.02)
- No effect on peritonitis incidence



Rodriguez-Carmona PDI 2013