Glucose Control in CKD patients with diabetes

유 태 현

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KOREAN ESRD REGISTRY

Prevalence of ESRD

United States
Renal Data System
2008 Annual Data Report

International Comparison In USRDS 2008

941.7 PMP
End of 2006

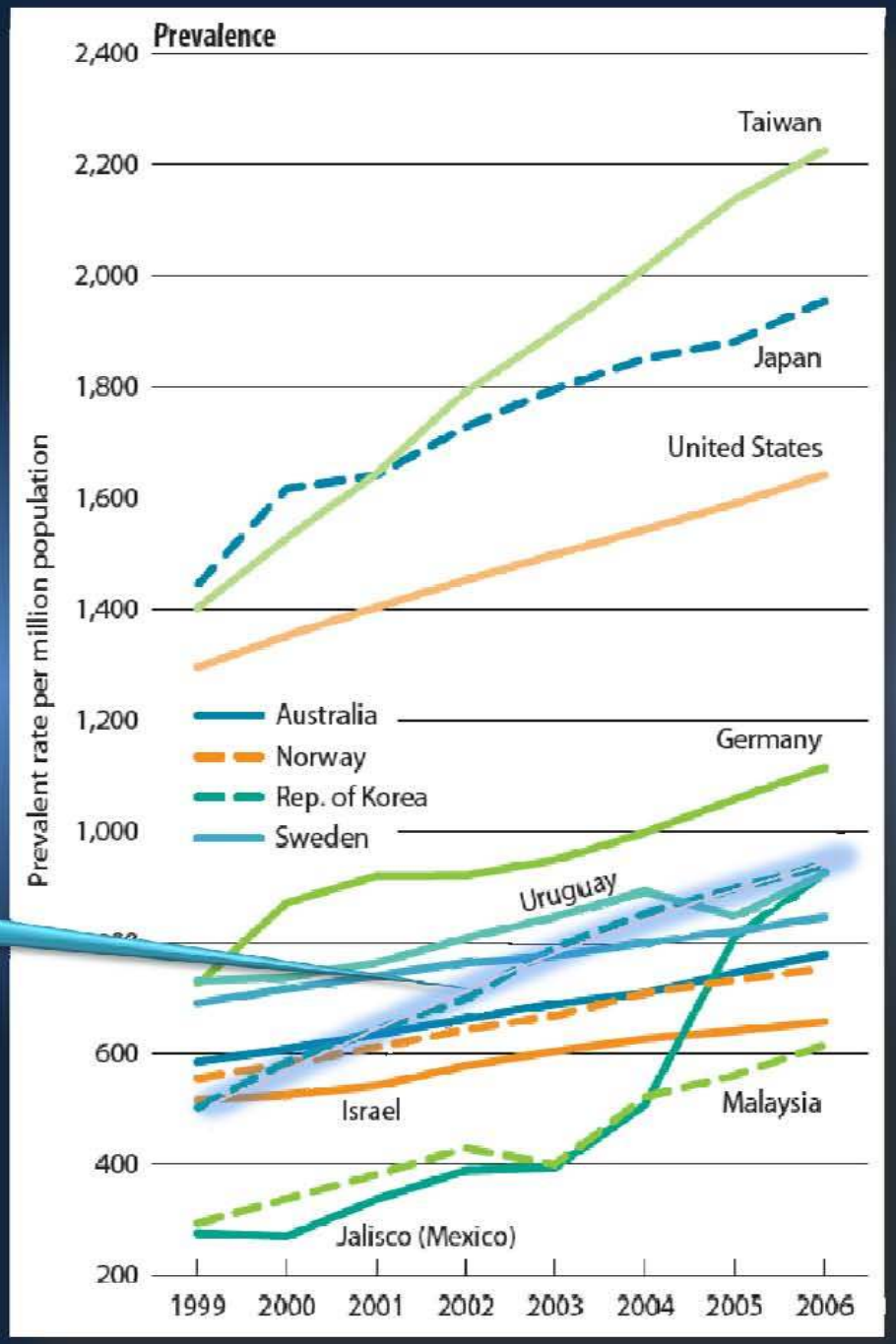
KOREAN ESRD REGISTRY

Changes of ESRD Prevalence

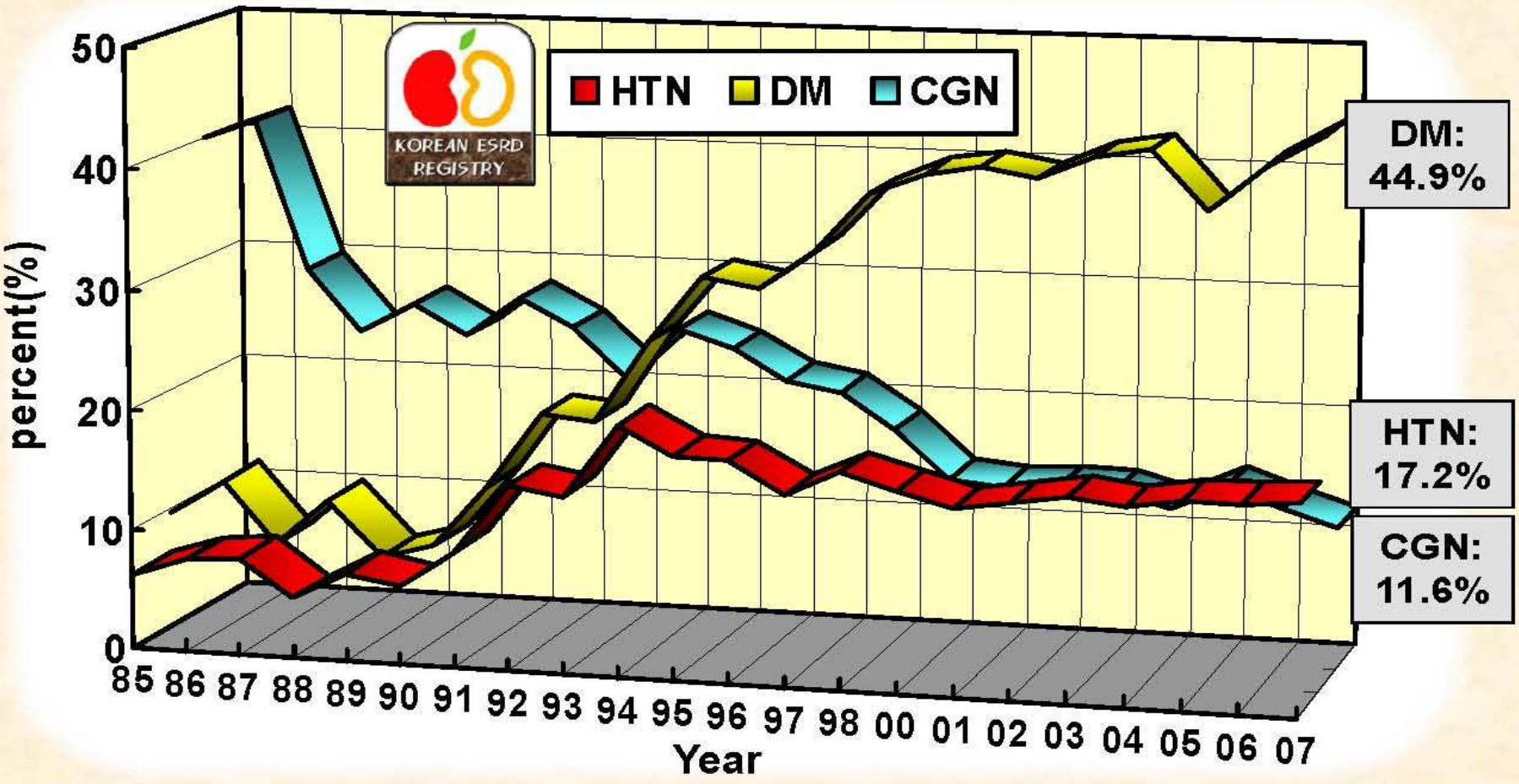
United States
Renal Data System
2008 Annual Data Report

International Comparison In USRDS 2008

941.7 PMP
2006



Three Major Causes of ESRD

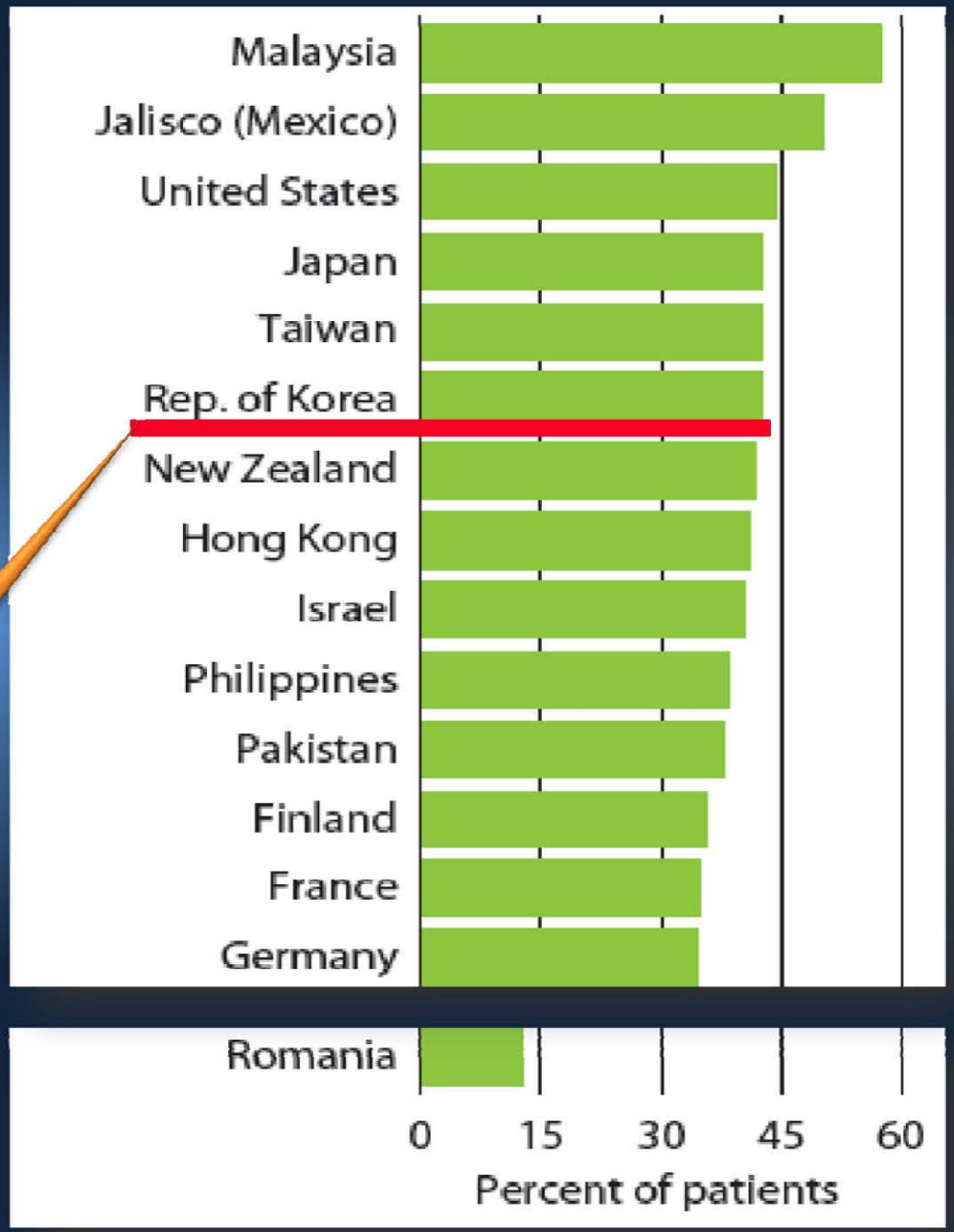


KOREAN ESRD REGISTRY

Diabetic ESRD

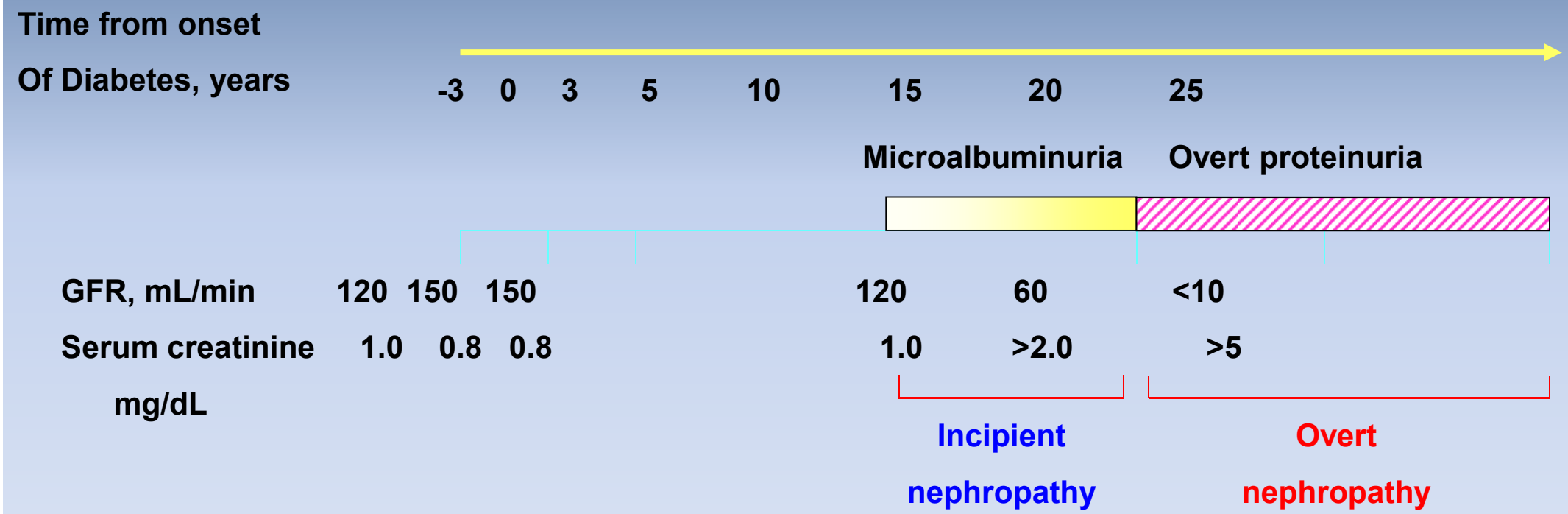
United States
Renal Data System
2008 Annual Data Report

International Comparison In USRDS 2008

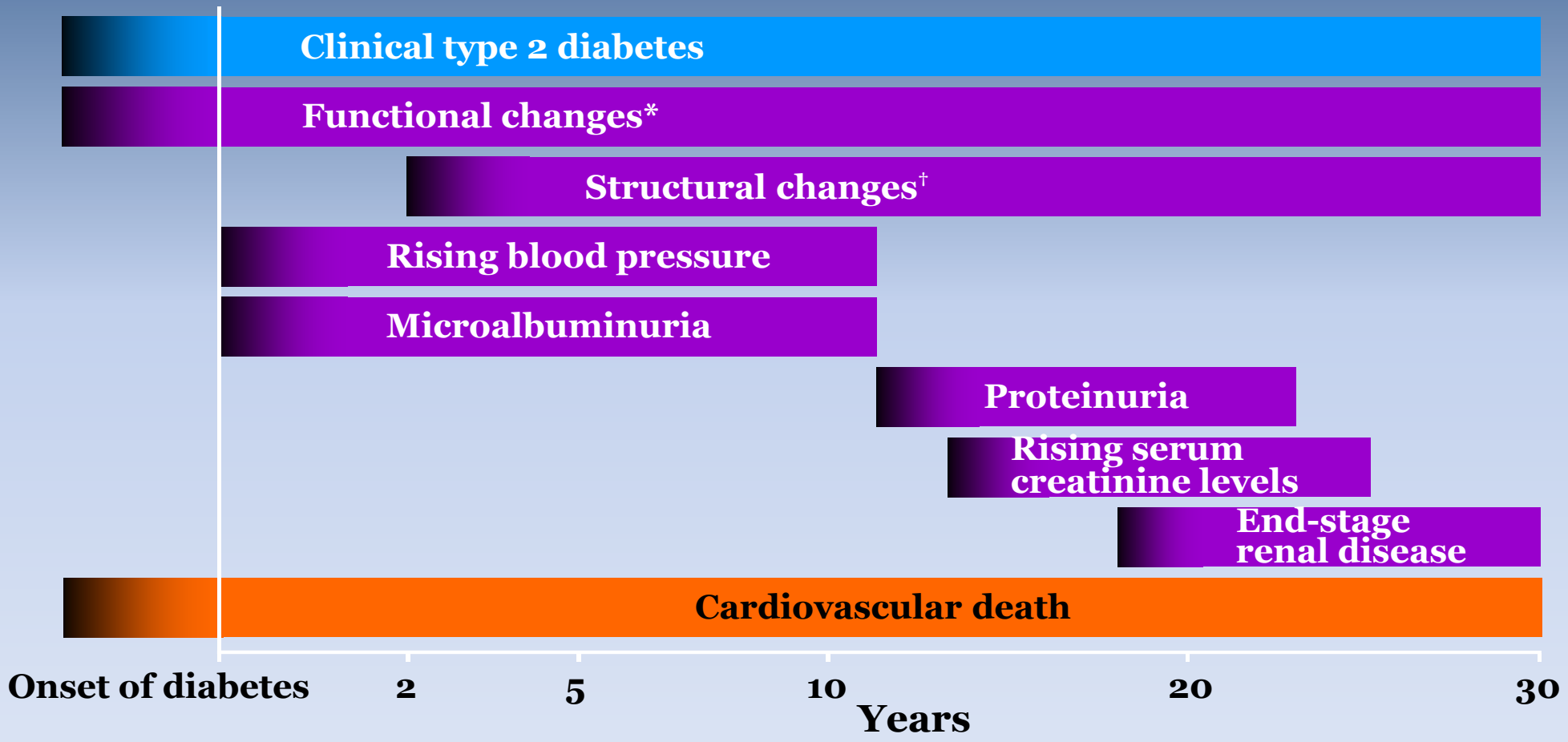


42.3%
2006

Natural History of Type 1 DN



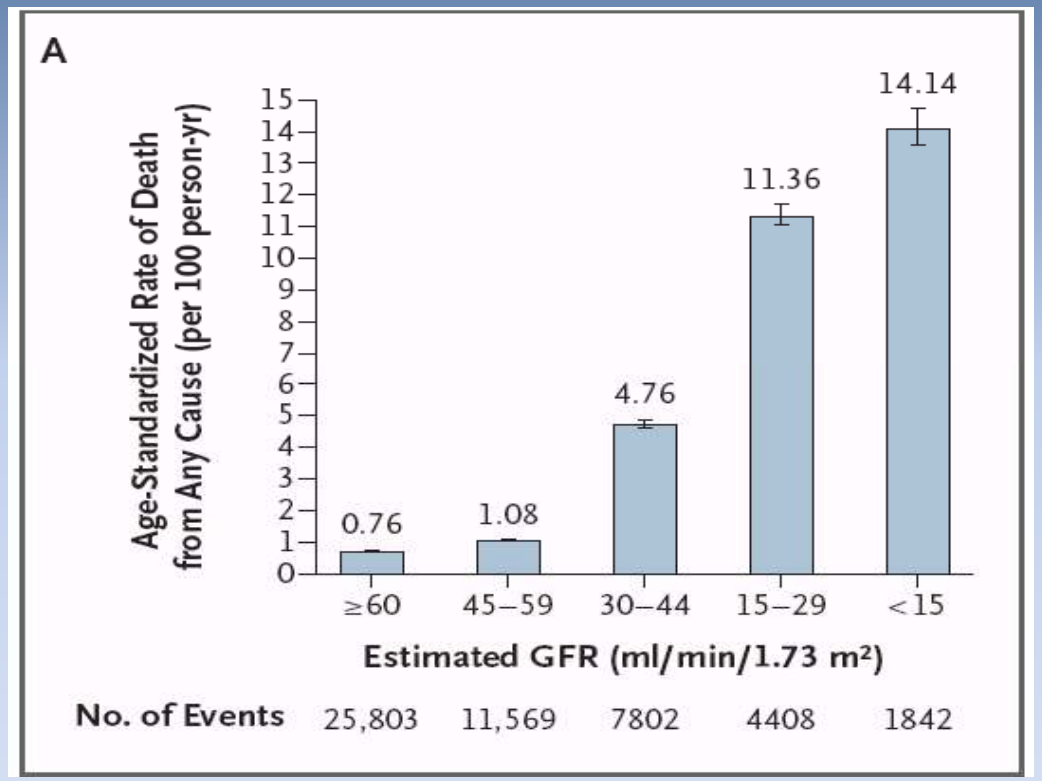
Natural History of Type 2 DN

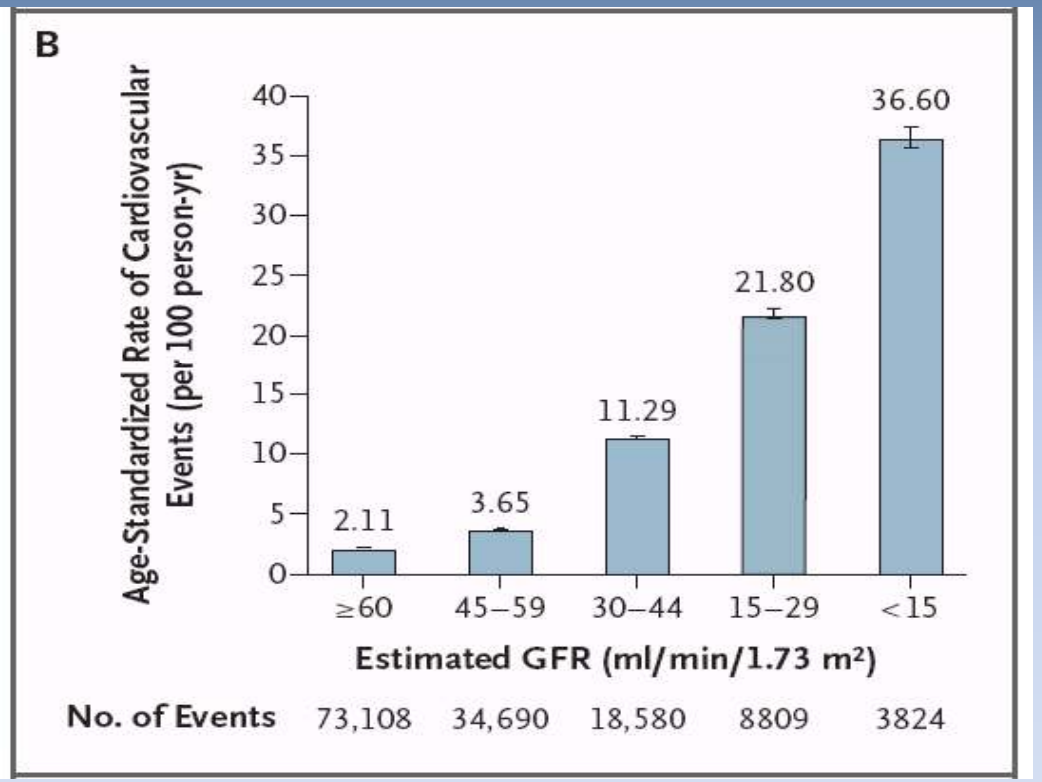


* Renal hemodynamics altered, glomerular hyperfiltration.

† Glomerular basement membrane thickening -, mesangial expansion -, microvascular changes +/-.

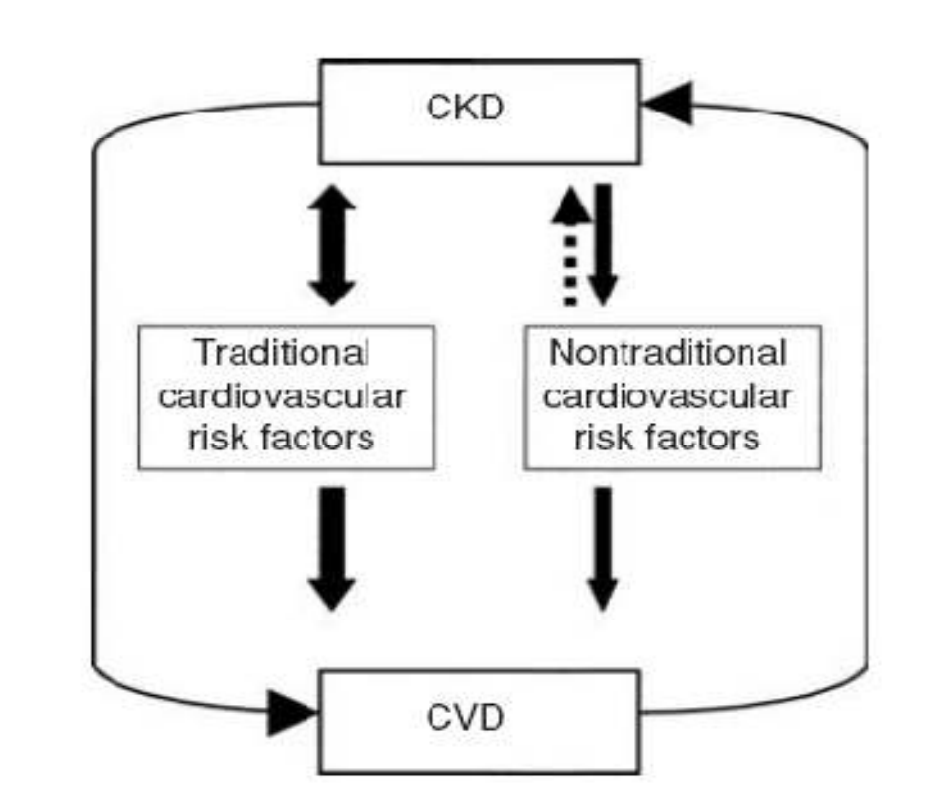
CKD: an Independent Risk Factor for CVD and Death





NEJM 351:1296-1305, 2004 from NHANES data

Cardiovascular complications in CKD



- Traditional risk factor
  - age
  - hypertension
  - dyslipidemia
  - smoking
  - diabetes
  - male gender
- Non-traditional risk factor
  - albuminuria
  - reduced GFR
  - anemia
  - inflammation
  - volume overload
  - abnormal Ca/P metabolism

Factors Affecting Glycemic Control in CRF

- Clearance of insulin
- Insulin resistance
- Insulin secretion
- Metabolic and nutritional complications in CRF
- Mode of dialysis
- Dialysate glucose absorption
- GI complications affecting intake and absorption
- Specific problems in DM patients

Clearance of Insulin

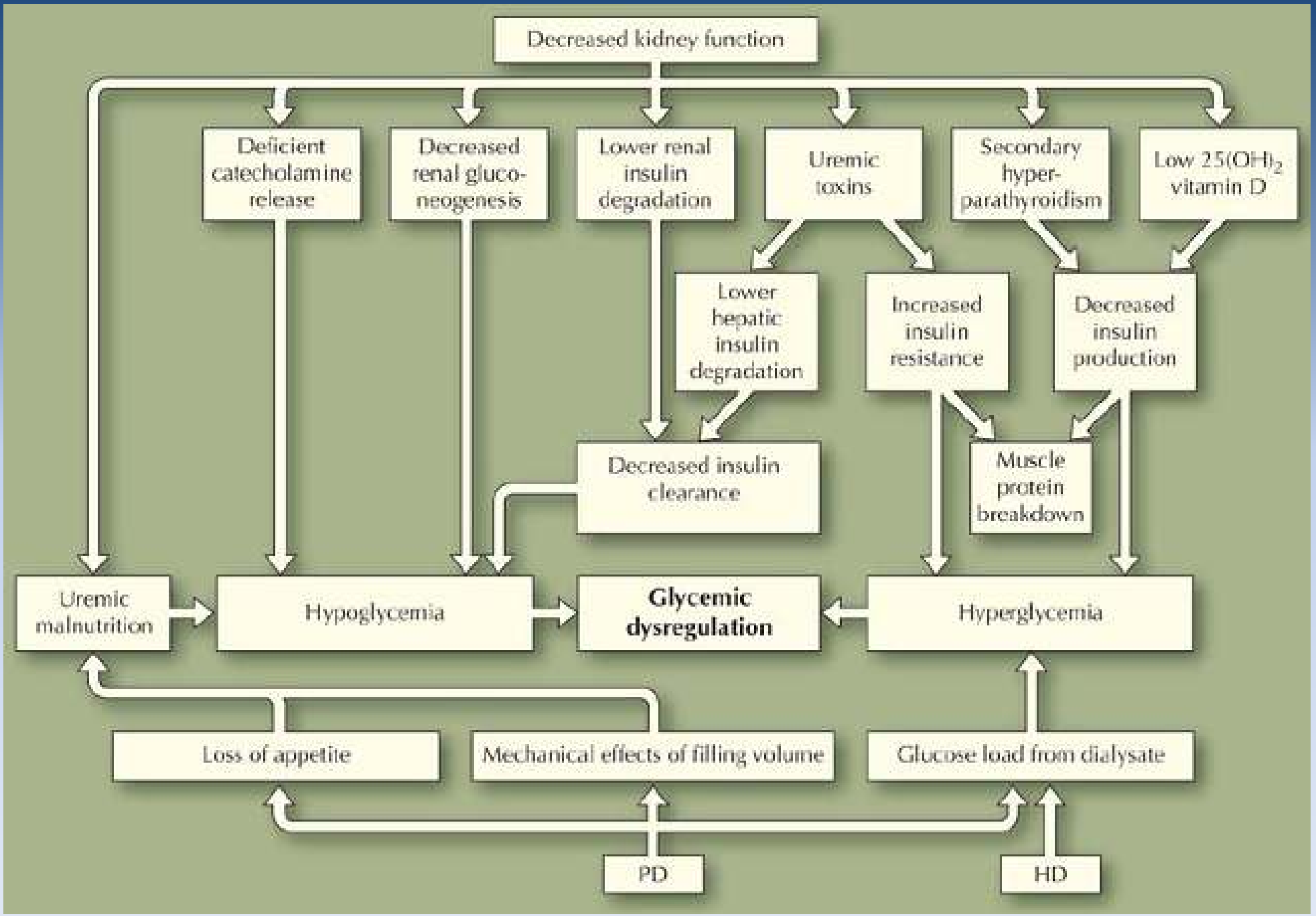
- Renal clearance of insulin
  - Glomerular filtration
  - Peritubular uptake and degradation
- Little change until GFR < 40 ml/min
- ↑Peritubular uptake until GFR < 15~20 ml/min
- Impaired degradation in liver and muscle
- Normalization of impaired insulin metabolism by dialysis

Insulin Resistance

- Common in patients with CRF
- Primary site of insulin resistance: Muscle
- Molecular site (?)
  - Oxidative and nonoxidative pathway
  - Muscle pyruvate dehydrogenase
- Uremic toxin
  - “Middle molecule”
  - Pseudouridine

Insulin Secretion

- Abnormalities in insulin secretion
- Pathogenesis: Calcium metabolism (?)
  - Hyperparathyroidism
  - Vitamin D deficiency
- Improvement by parathyroidectomy (medical or surgical) and by vitamin D3 replacement


Decreased kidney function
Deficient catecholamine release
Decreased renal gluco-neogenesis
Lower renal insulin degradation
Uremic toxins
Secondary hyper-parathyroidism
Low 25(OH)2 vitamin D
Lower hepatic insulin degradation
Increased insulin resistance
Decreased insulin production
Decreased insulin clearance
Muscle protein breakdown
Uremic malnutrition
Hypoglycemia
Glycemic dysregulation
Hyperglycemia
Loss of appetite
Mechanical effects of filling volume
Glucose load from dialysate
PD
HD

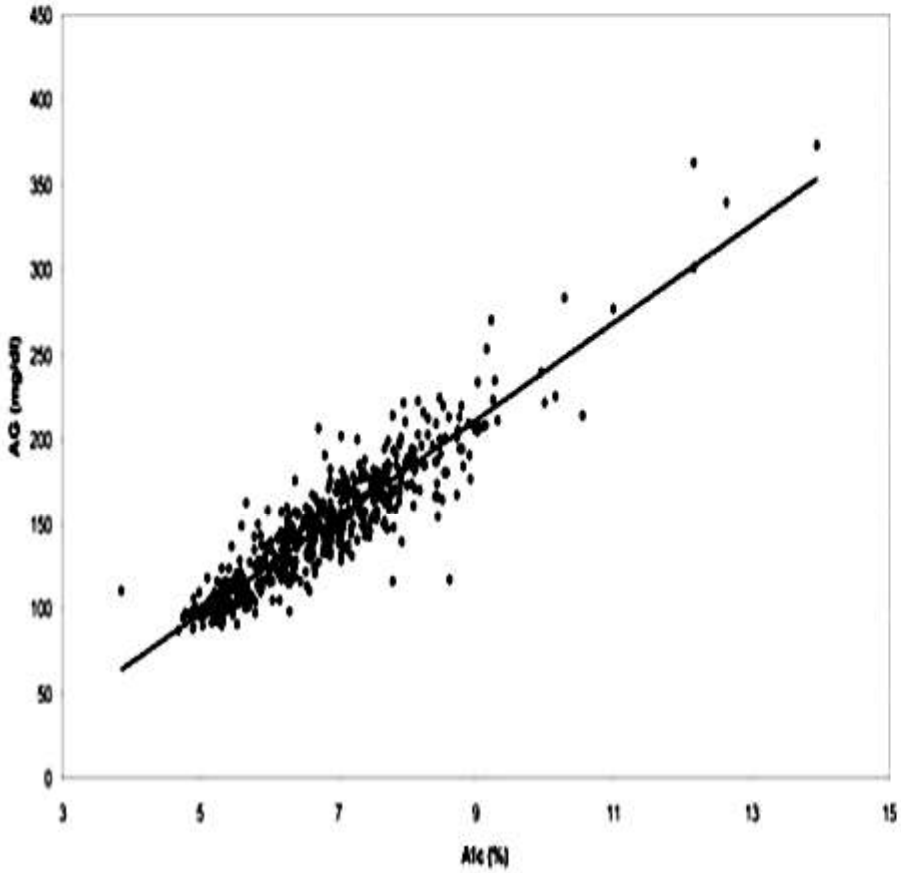
Translating the A1C assay into estimated average glucose values

Day-to-day management is guided by self-monitoring of capillary glucose concentrations (milligrams per deciliter or millimoles per liter).

(AG(mg/dl) = 28.7 x A1C - 46.7, R(2) = 0.84, P < 0.0001), allowing calculation of an estimated average glucose (eAG) for A1C values.

A1C levels can be expressed as eAG for most patients with type 1 and type 2 diabetes.

(Diabetes Care, 2008)



HbA1C(%)	Mg/dL	mmol/L
5	97	5.4
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

(Diabetes Care, 2008)

Glycated Hemoglobin (I)

- Series of minor Hb formed by the adduction of various CHO molecules to Hb
- Minor Hb components
  - HbA1a (1.6%), HbA1b (0.8%), HbA1c (4.0%)
- Glycation rate
  - Temperature
  - Hb concentration
  - Glucose concentration
  - Length of exposure to glucose

Glycated Hemoglobin (II)

- **HbA1c**
  - Largest fraction
  - Formed by nonenzymatic posttranslation glycation in two-step reaction
- Measurement of HbA1c
  - Depend on the charge on HbA1c
  - Ion-exchange chromatography
  - High-performance liquid chromatography
  - Agar-gel electrophoresis

Glycated Hemoglobin (III)

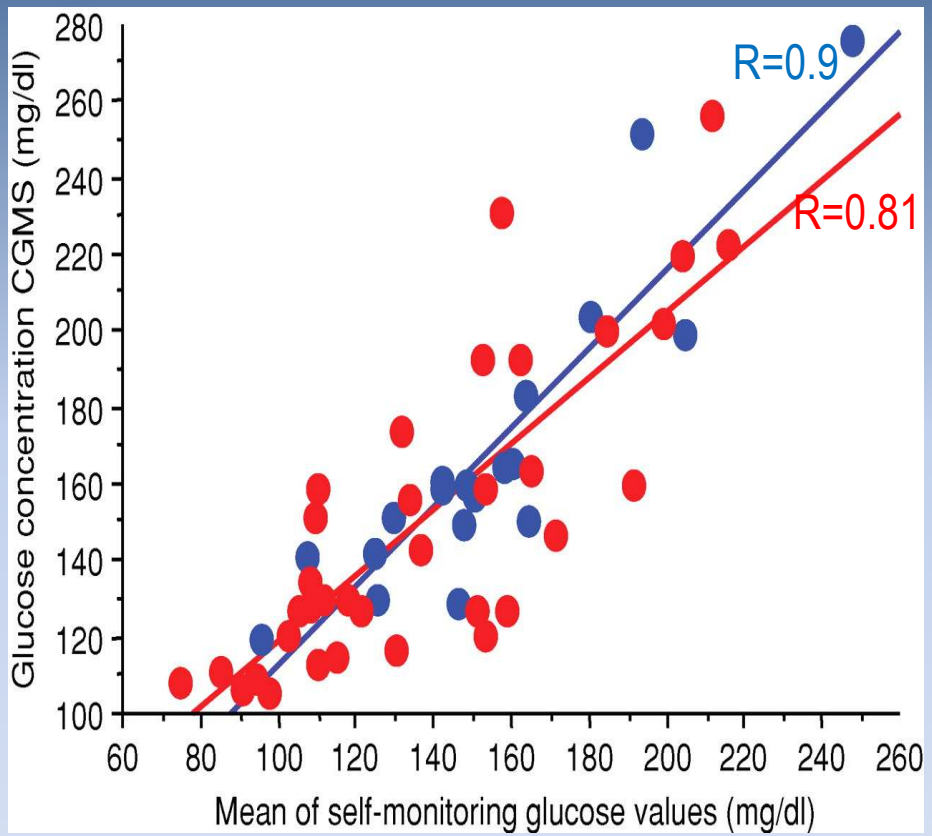
- Glycation occurs throughout the lifetime of RBCs
- The oldest cells being the most glycated
- **HbA1c levels**

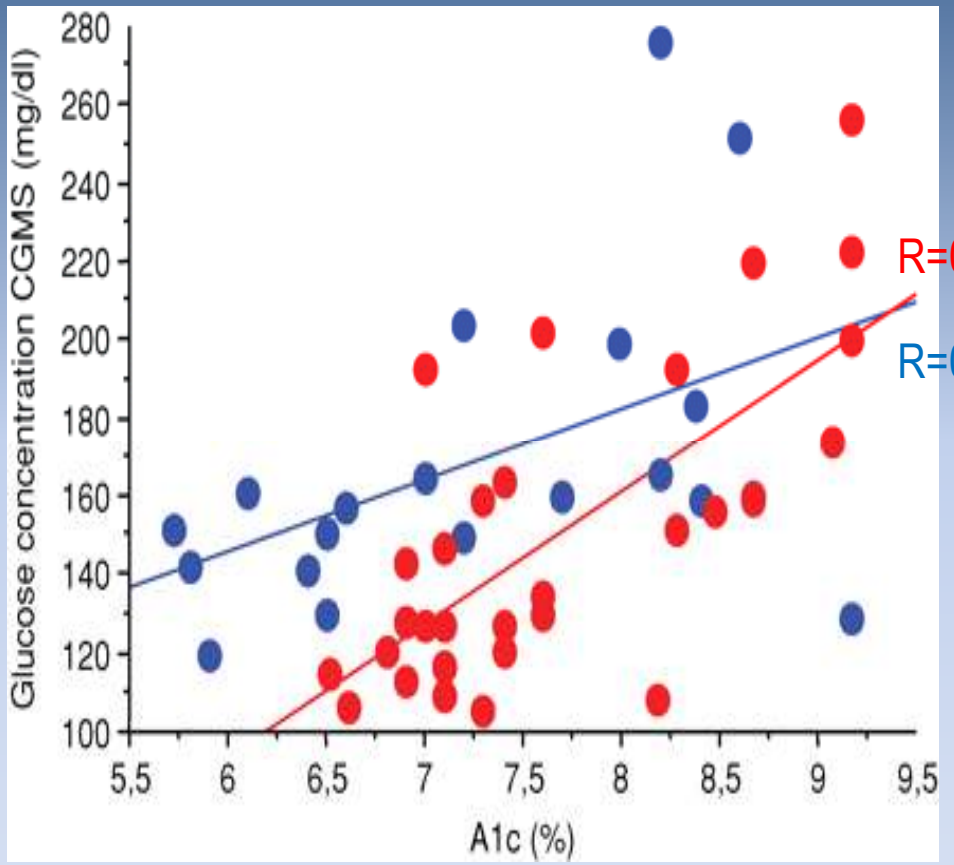
-30 days	50%
30-60 days	25%
60 days-	25%

HbA1c in CRF

- Less reliable in patients with renal failure
- High urea levels (more than 84 mg/dL)
  Form cyanate → Isocyanic acid (reactive form)
  → Carbamylated Hb
  → Falsely high levels of HbA1c in charge-dependent assay
- Acidosis: Increase in the rate of HbA1c formation
- Reduced RBC survival and iron deficiency
- Dilution from the frequent blood transfusion

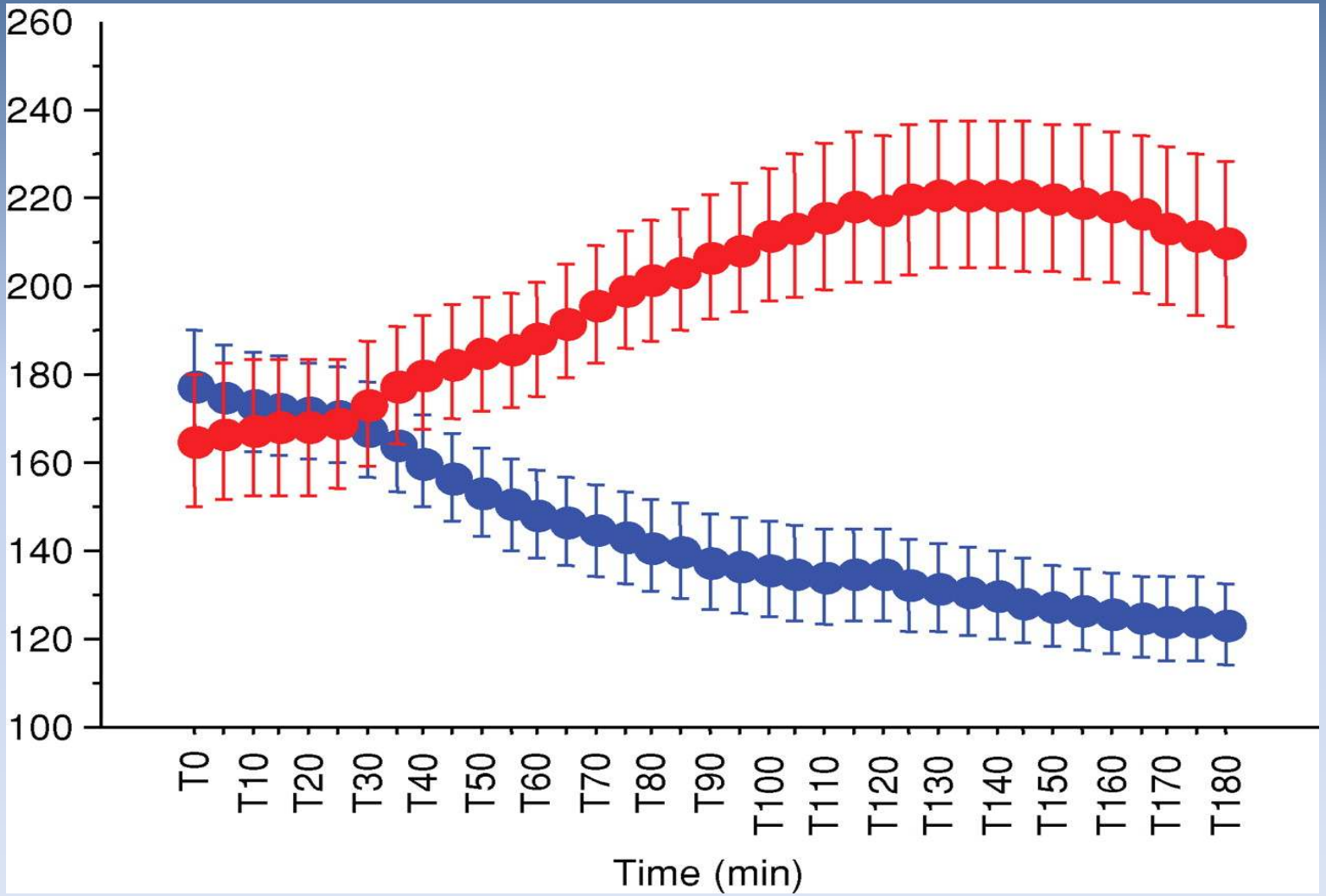
Correlation between mean glucose obtained through CGMS and glucose meters in HD T2 (blue circles) and non-HD T2 controls (red circles)





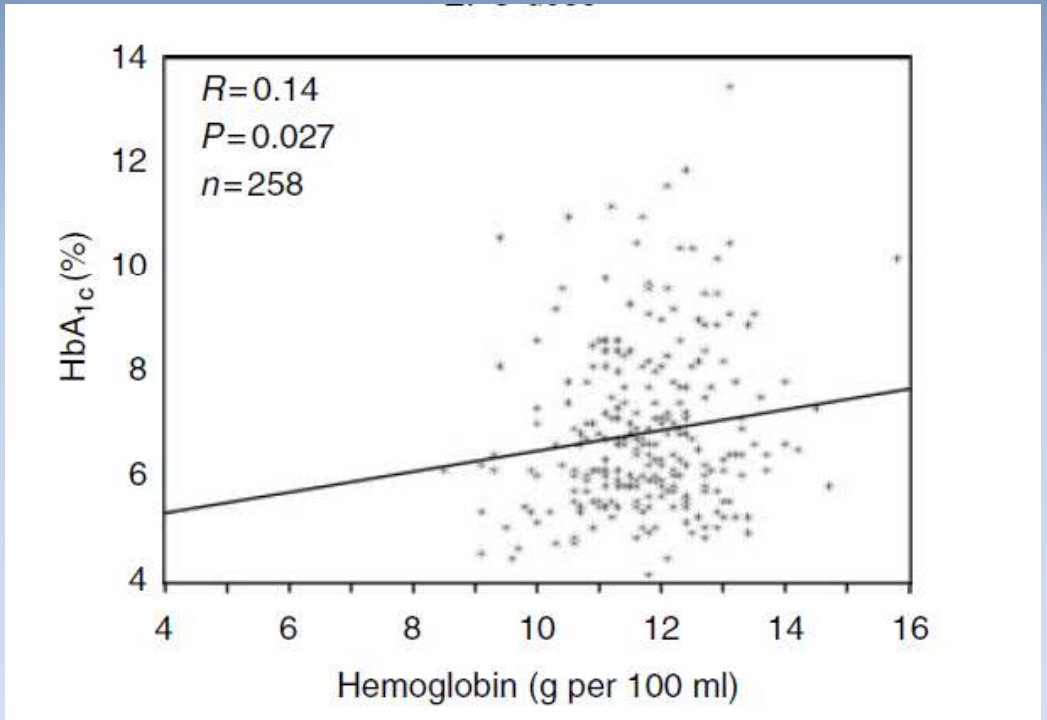
(Nephrol Dial Transplant, 2009)

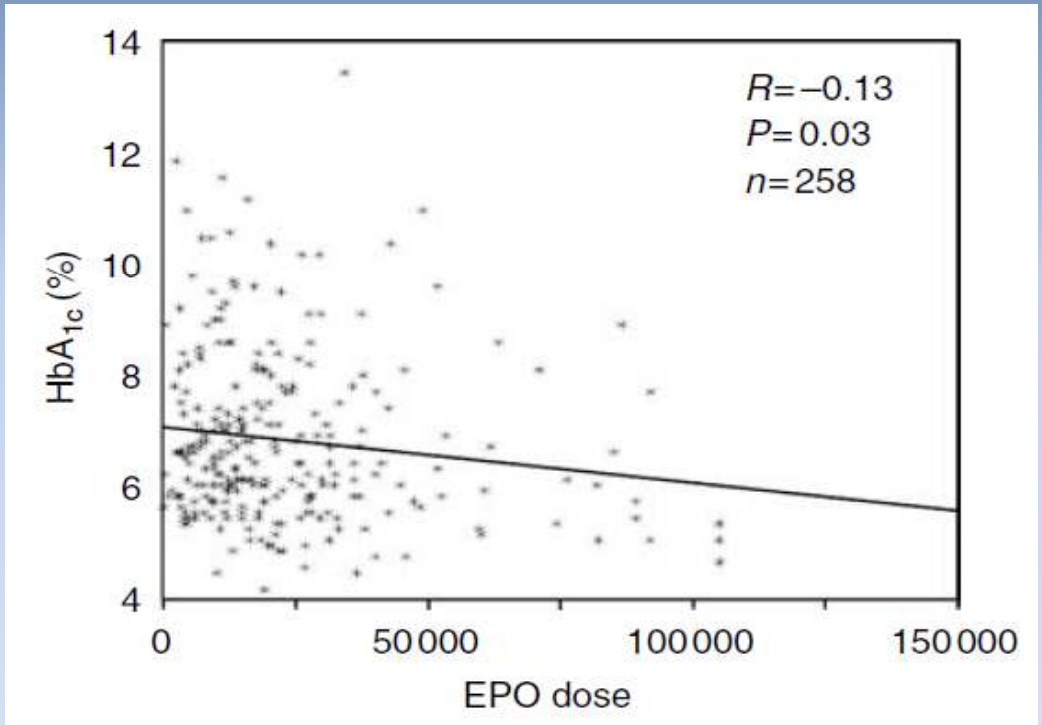
Glucose concentration in the first 3 h of the dialysis session (blue circles) or equivalent time without dialysis (red circles)



(Nephrol Dial Transplant, 2009)

Impact of hemoglobin concentration and EPO dose on HbA1C in diabetic ESRD





(Kidney Int, 2008)

Table 1. Diagnostic Tests to Assess Integrated Glucose Control in Patients With Diabetes Mellitus

Diagnostic Test	Glycemic Control Period	Conditions Affecting Interpretation	Advantages	Disadvantages
Hemoglobin A_{1c}	2-3 mo	Hemoglobinopathies, diseases of shortened erythrocyte life span	Used in major trials that determined thresholds of glycemic control. Routine testing available in most clinical laboratories	No information about short-term glucose control
Fructosamine	2-3 wk	Proteinuria, dysproteinemias, malnutrition, thyroid abnormalities, liver disease, pregnancy, steroid therapy	Unaffected by disease states affecting hemoglobin	Reference levels lacking Testing not offered routinely by most clinical laboratories
Glycated albumin	2 wk	Proteinuria, dysproteinemias, malnutrition, thyroid abnormalities, liver disease, pregnancy, steroid therapy	Unaffected by disease states affecting hemoglobin	Reference levels lacking Testing not offered routinely by most clinical laboratories

Fructosamine

- Measure of glycated serum proteins
- Glycation of serum albumin: 90%
- The rate of stable ketoamine formation
  4~5 times faster than HbA1c
- Reflects glycemia during a period of 2~3 weeks
- Measurement of fructosamine
  - Colorimetric assay (Redox dye)
  - Affinity chromatography
  - Immunoassay

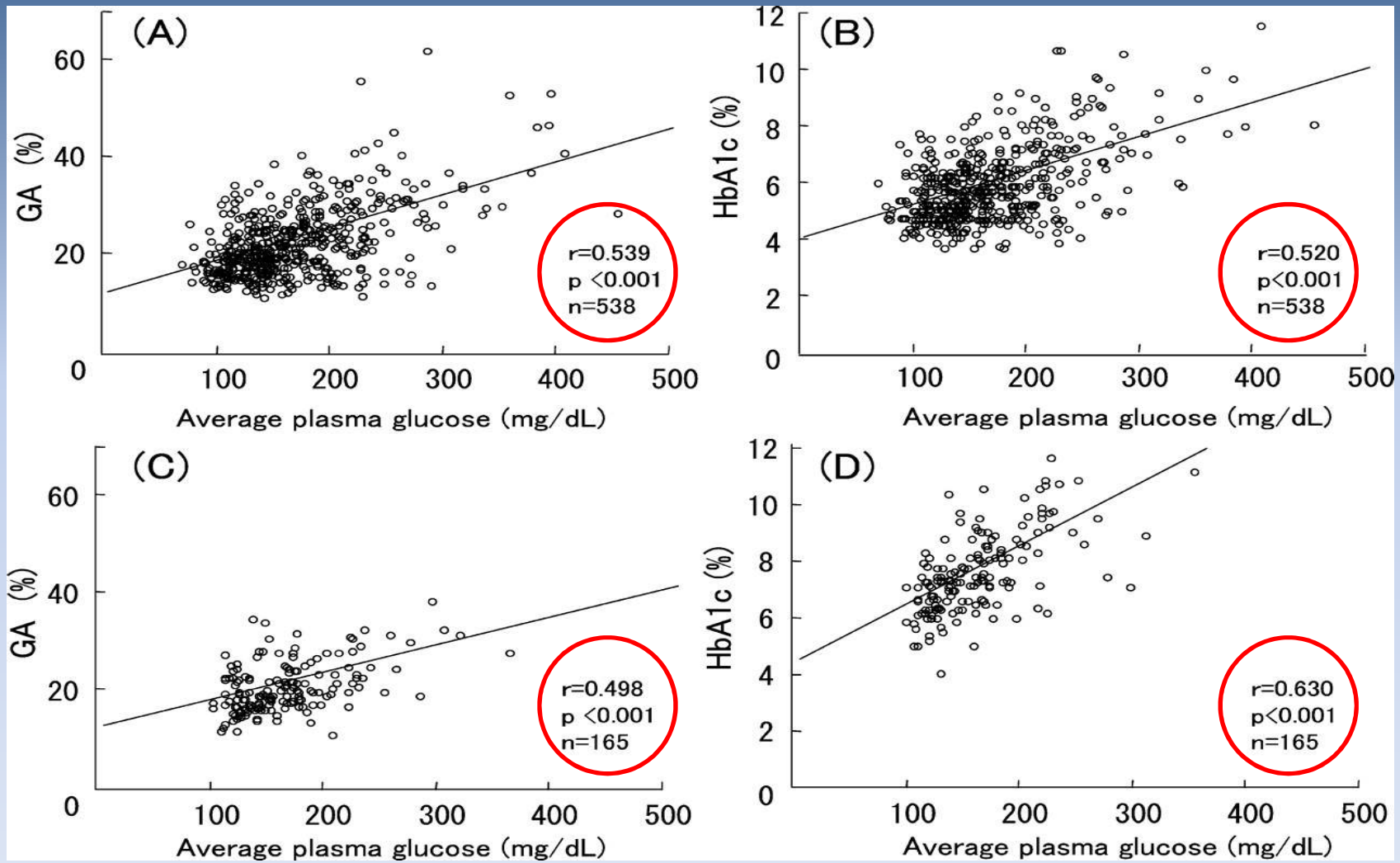
Fructosamine in CRF

- Less reliable as with HbA1c
- High urate levels in CRF
  → Interfere with the fructosamine assay
  → Falsely high fructosamine levels
- Affected by protein turnover
  PD: Protein loss through the peritoneum
  HD: Aminoacids loss into the dialysate
  HD: Potential catabolic factor stimulating protein breakdown

HbA1c vs. Fructosamine in Patients with DM and CRF

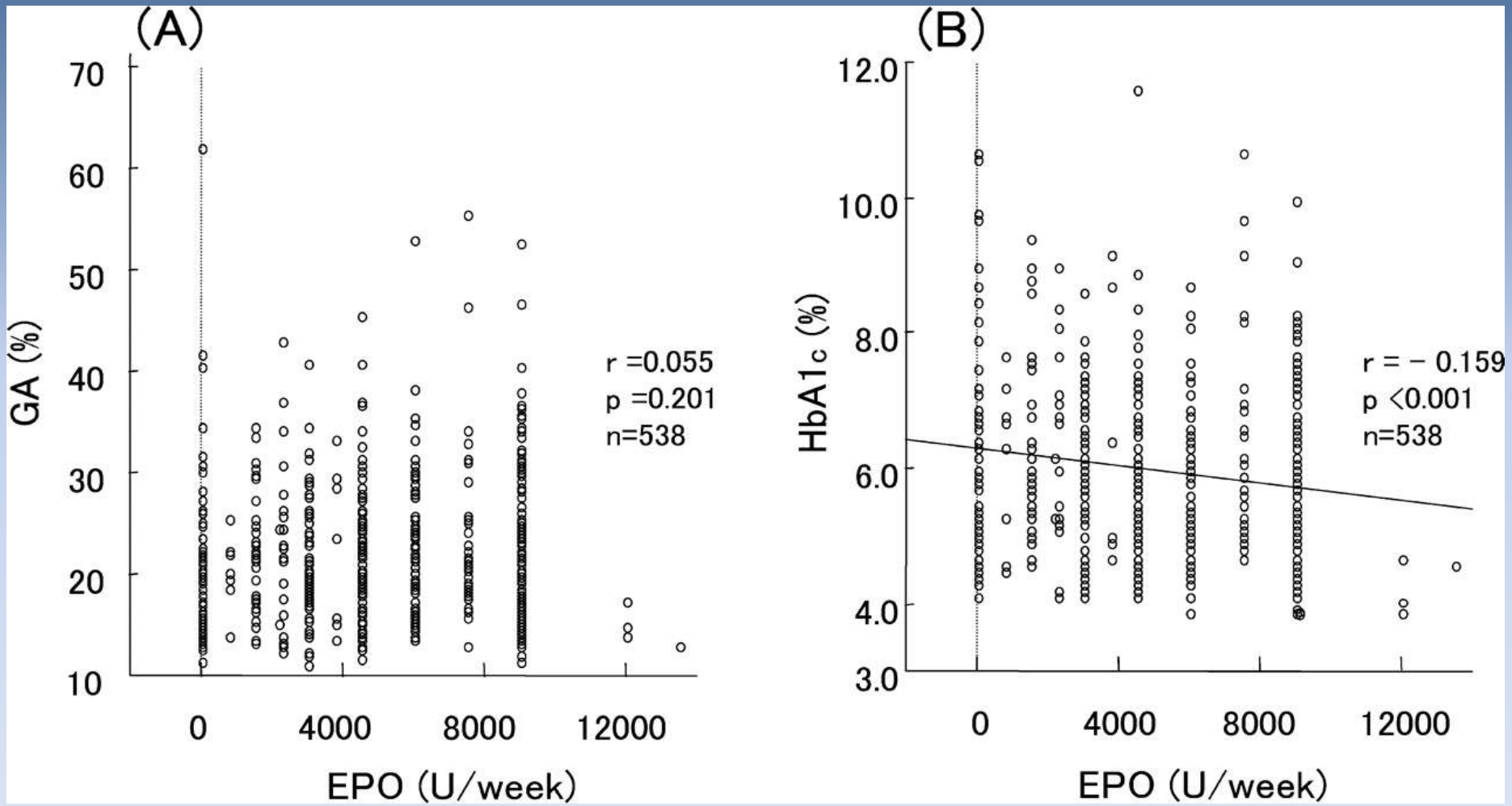
Reference	Treatment Modality	No. of Patients	Weeks Glucose Level Determined For	Correlation Between Mean/Median Blood Glucose Level and	
				HbA_{1c}	Fructosamine
Bilo et al[53]	CAPD	13	4	r = 0.71, $P < 0.005$	R = 0.68, $P < 0.01$
Nunoi et al[54]	HD	14	3	r = 0.703, $P < 0.001$	r = 0.372, P not significant
Ichikawa et al[55]	HD	31	2	r = 0.6705, $P < 0.001$	r = 0.4615, $P < 0.01$
			4	r = 0.692, $P < 0.001$	r = 0.4782, $P < 0.001$
Morgan et al[56]	Managed conservatively (low clearance)	5	6	r = 0.57, $P = 0.01$	r = −0.1, $P = 0.71$ (not significant)
	CAPD	6			
	HD	3			
Joy et al[58]	HD	23	1	r = 0.58, $P < 0.05$	r = 0.345, $P = 0.11$ (not significant)

Correlation between the average plasma glucose (PG) values and glycated albumin (GA) or glycated hemoglobin (HbA1c) in hemodialysis (HD) patients with diabetes and in patients with diabetes and without chronic renal failure (CRF)



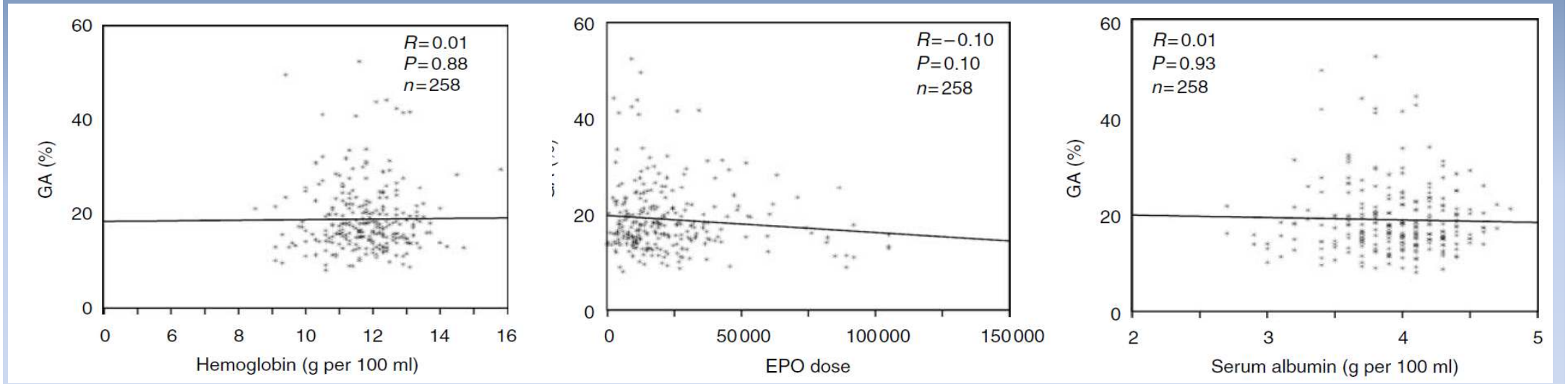
(J Am Soc Nephrol, 2007)

Correlation of weekly doses of recombinant human erythropoietin with GA and HbA1c levels



(J Am Soc Nephrol, 2007)

Impact of hemoglobin concentration and EPO dose on GA in diabetic ESRD



(Kidney Int, 2008)

Impact of glycated albumin on survival of diabetic patients on hemodialysis : A 3-year observational study (I)

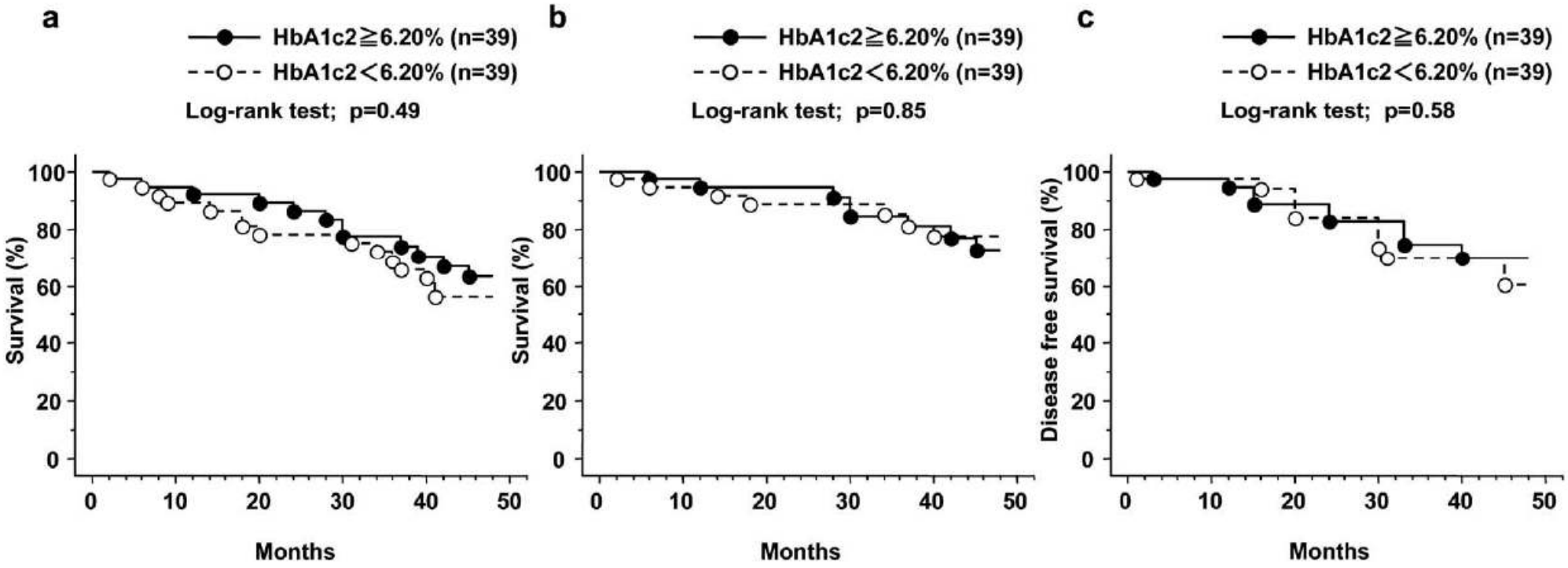


Figure 2. The Kaplan-Meier survival curves of all-cause mortality (a), CV mortality (b) and development of CV diseases (c) in the higher HbA1c2 (HbA1c ≧ 6.20%) group and the lower HbA1c2 (HbA1c < 6.20%) group.

(Intern Med, 2007)

Impact of glycated albumin on survival of diabetic patients on hemodialysis : A 3-year observational study (II)

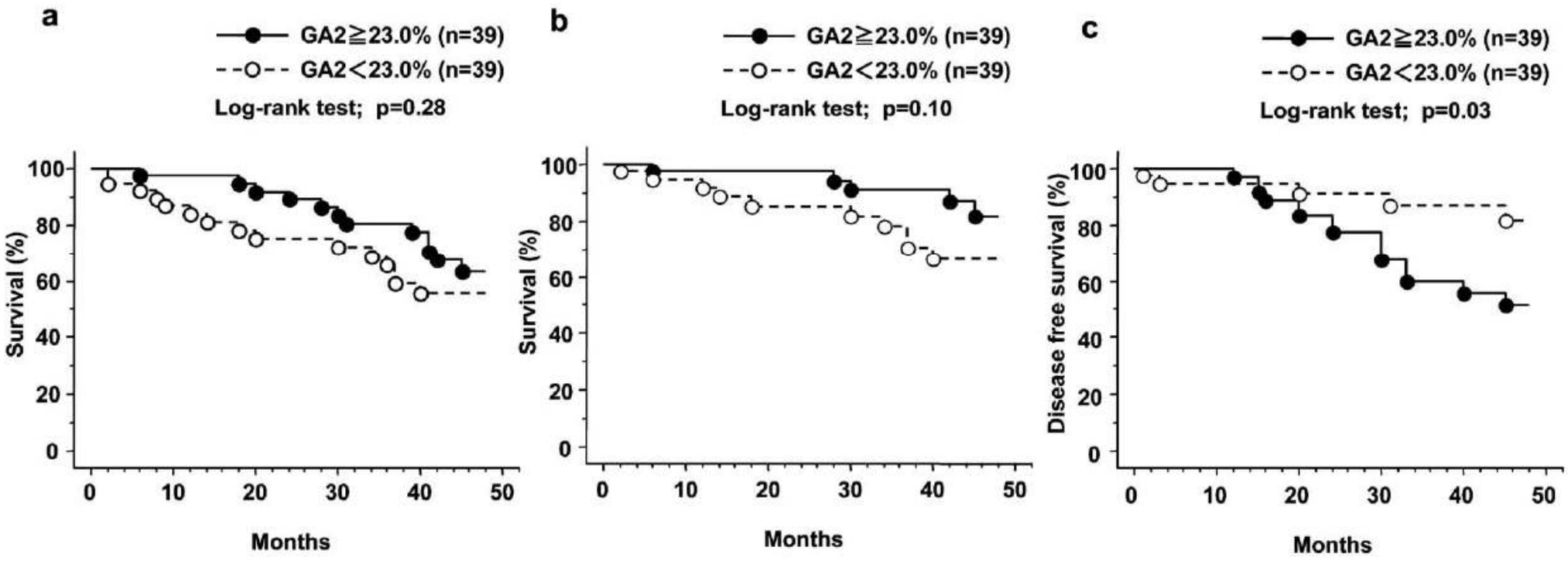
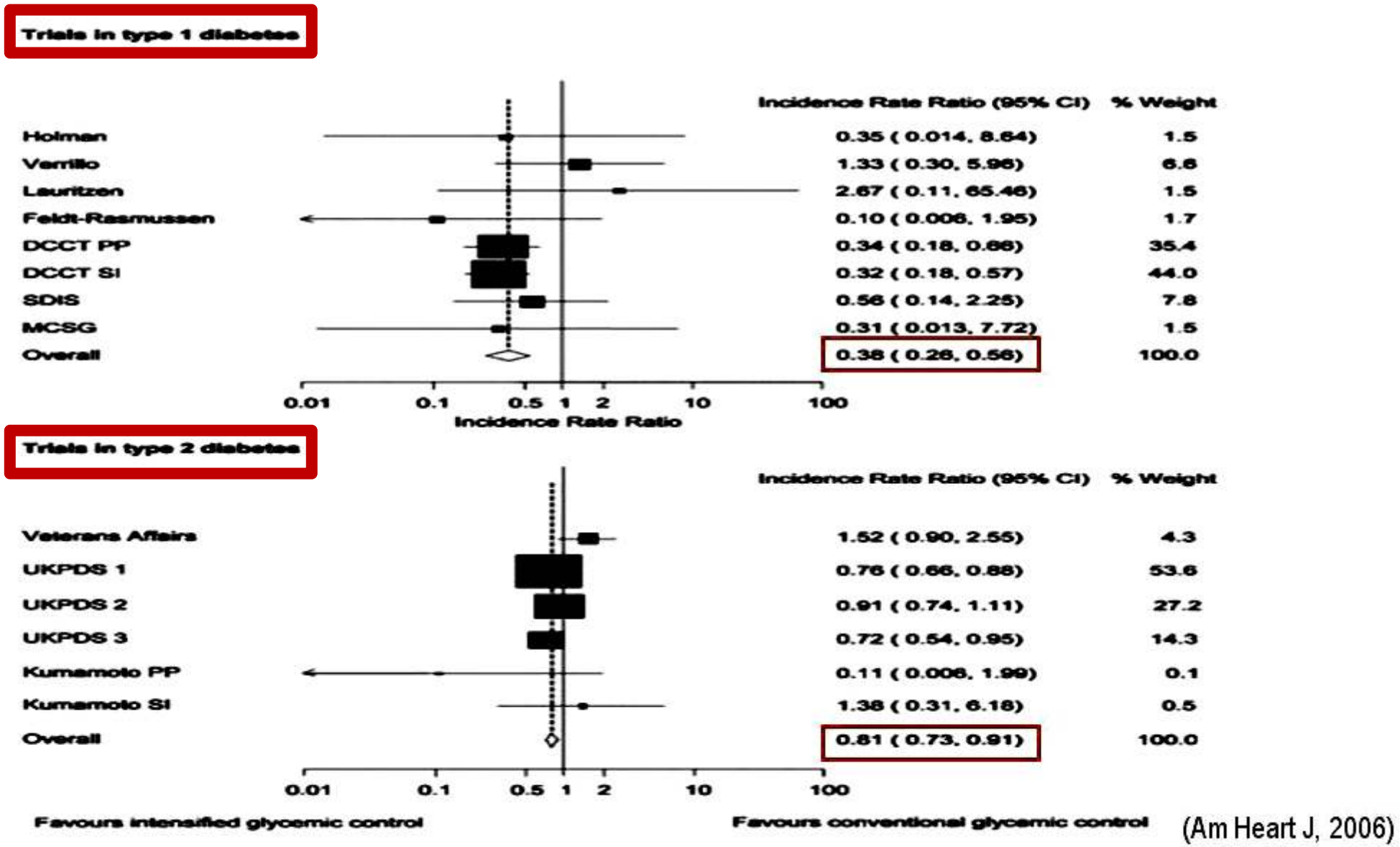


Figure 3. The Kaplan-Meier survival curves of all-cause mortality (a), CV mortality (b) and development of CV diseases (c) in the higher GA2 (GA ≧ 23.0%) group and the lower GA2 (GA < 23.0%) group.

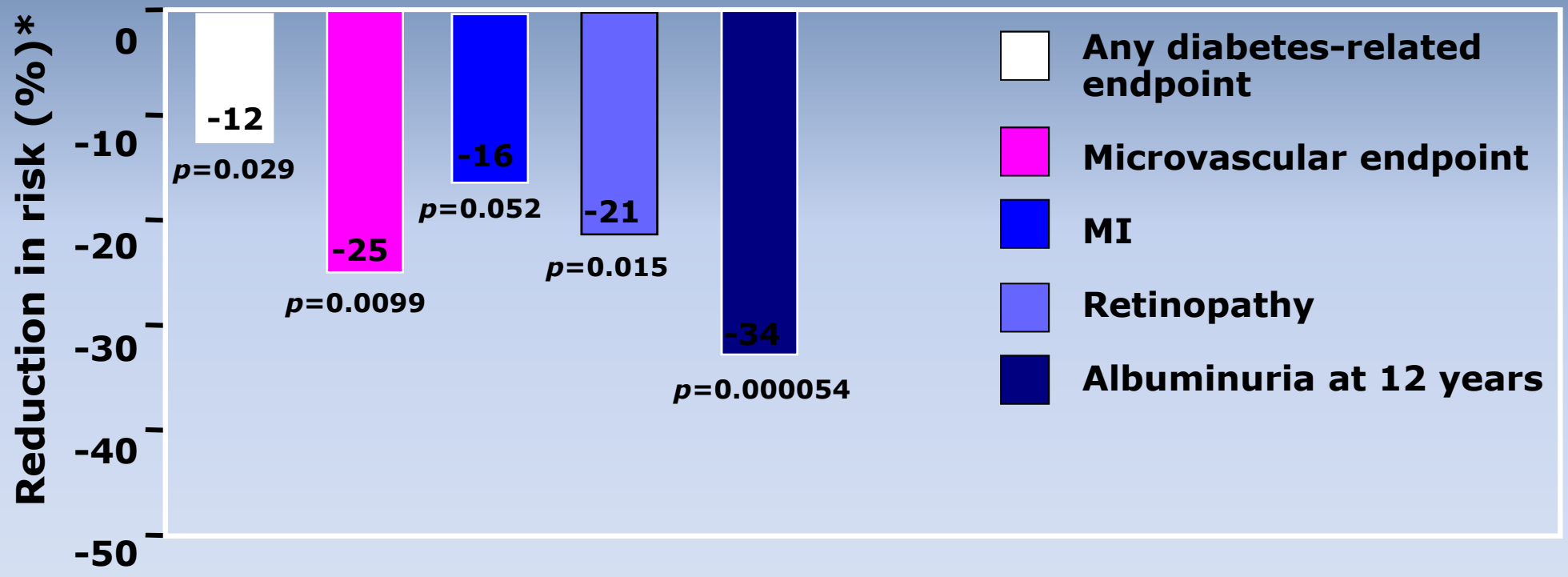
(Intern Med, 2007)

Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials



(Am Heart J, 2006)

United Kingdom Prospective Diabetes Study (UKPDS)



UKPDS. *Lancet*. 1998;352:837-853.

KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and CKD

GUIDELINE 2: MANAGEMENT OF HYPERGLYCEMIA AND GENERAL DIABETES CARE IN CKD patients

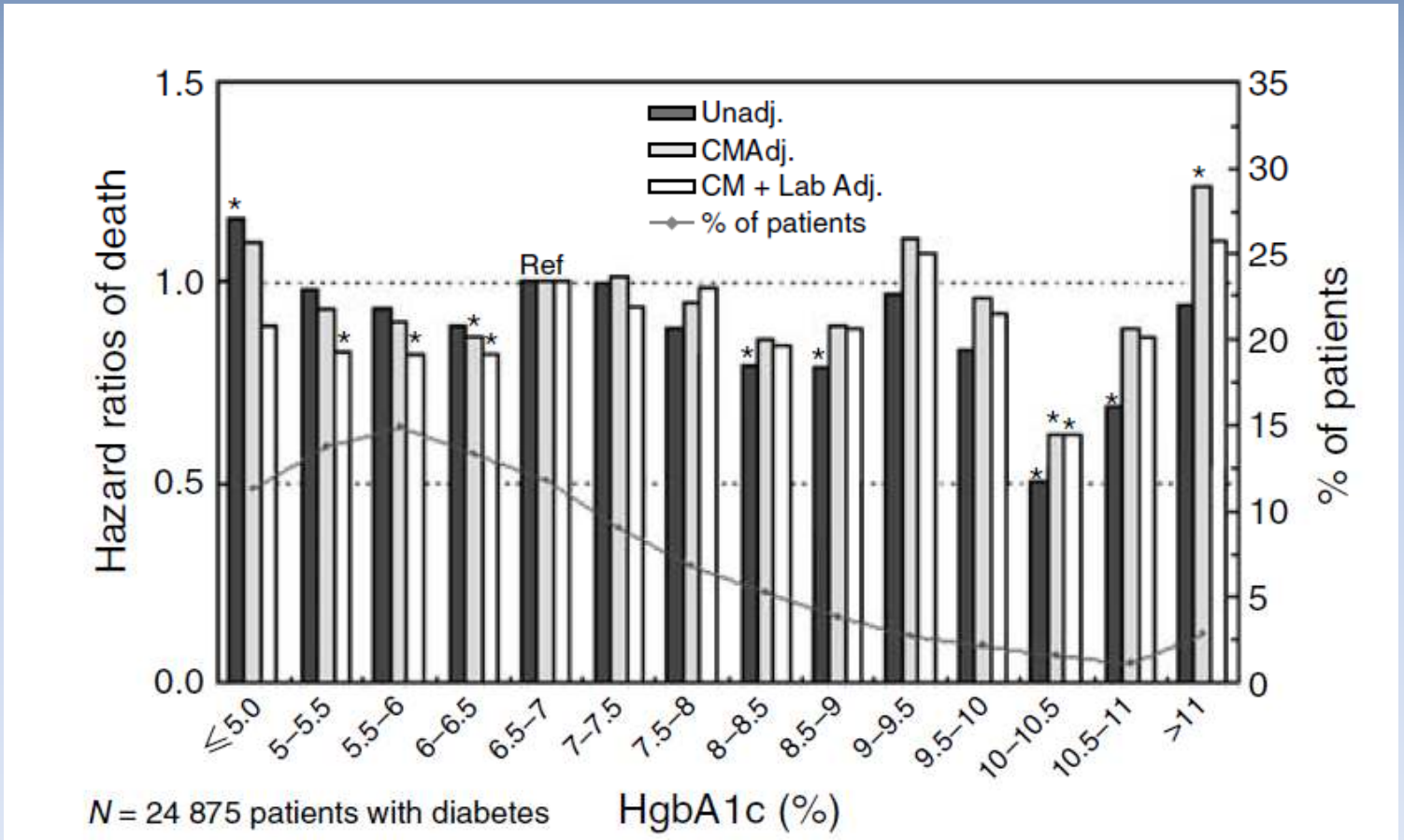
Intensive treatment of hyperglycemia prevents DKD and may slow the progression of established kidney disease.

2.1 Target HbA_{1c} for people with diabetes should be < 7.0%, irrespective of the presence or absence of CKD. (A)

(Am J Kid Dis, 2007)

Glycemic control and survival in HD (I)

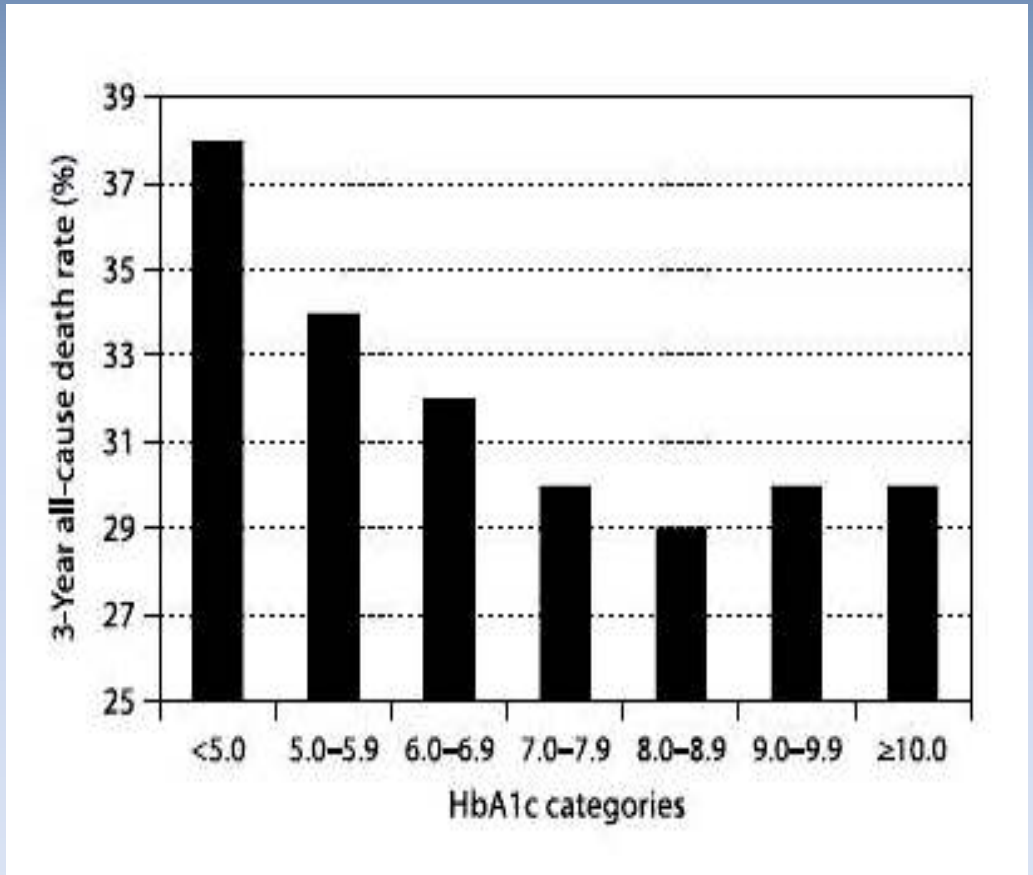
- 38,701(50.8%)/76,178 HD patients in FMC center
- All cause mortality for 12-month follow up



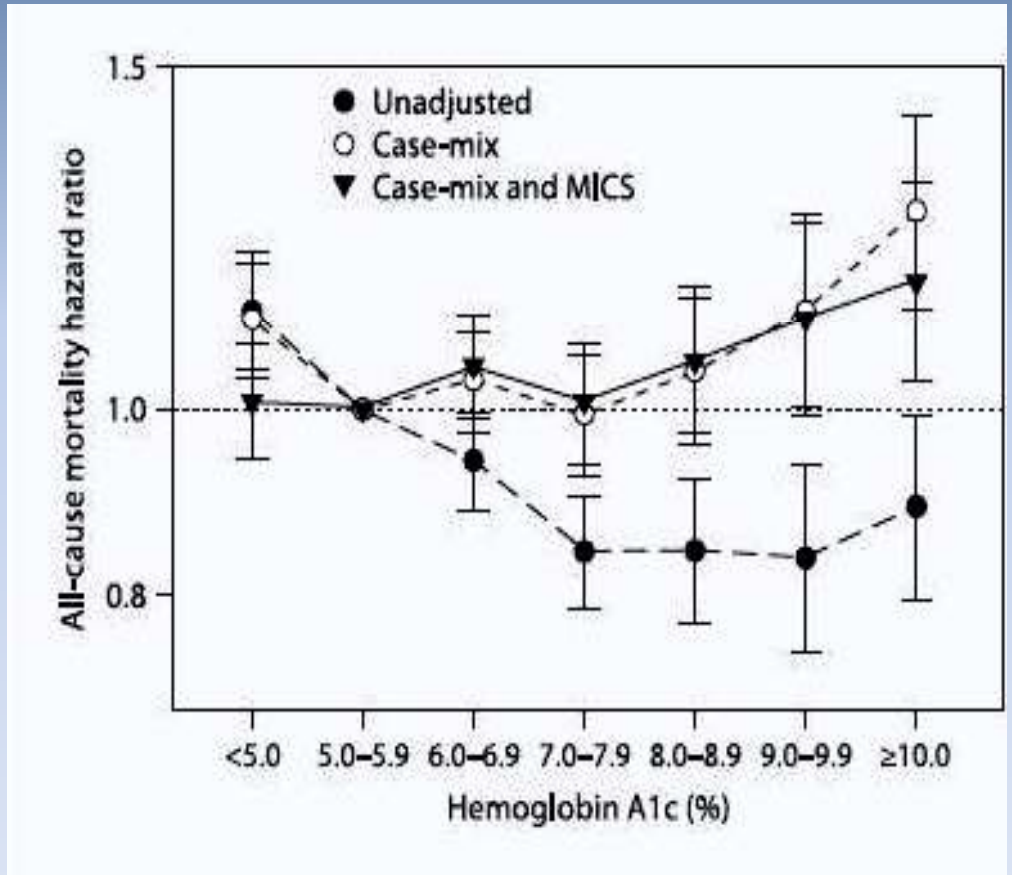
Williams ME, Kidney Int 2006

Glycemic control and survival in HD (II)

23,618 diabetic HD patients in USRDS database, 3yrs F/U



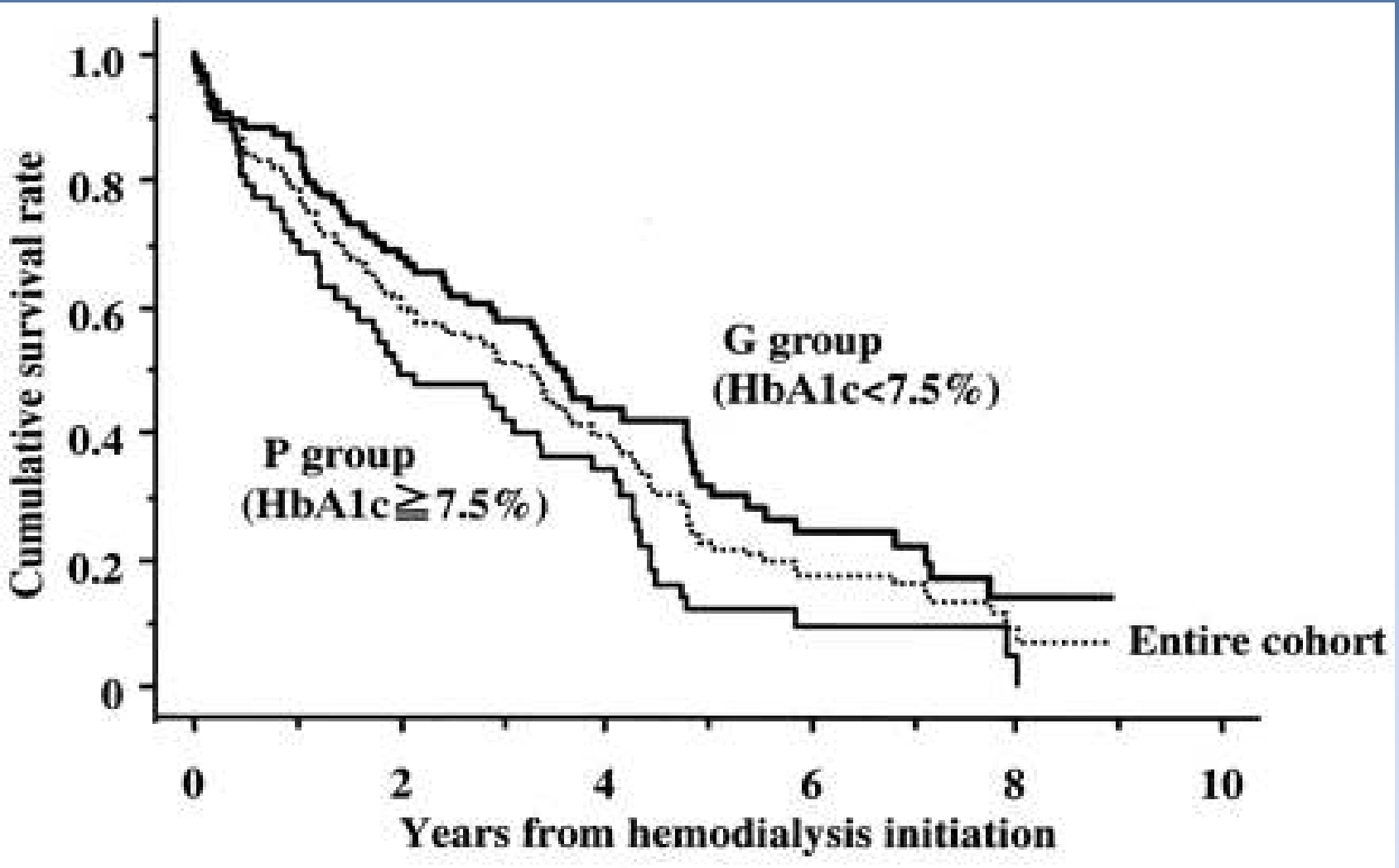
Unadjusted mortality rate



Adjusted mortality rate

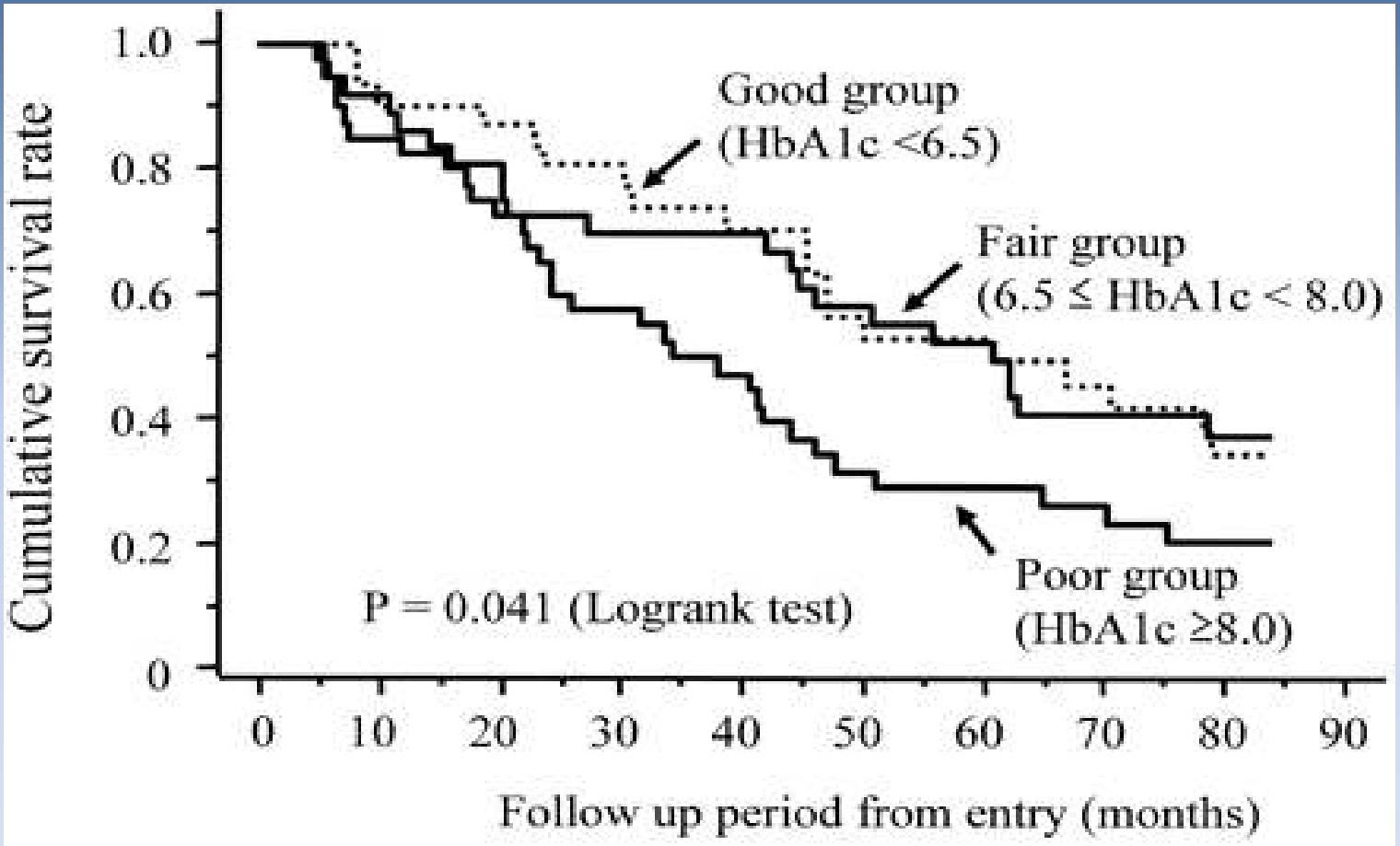
(Diabetes Care, 2007)

Glycemic control and survival in HD (III)



(Diabetes Care, 2001)

Impact of glycemic control on survival of diabetic patients on hemodialysis : A 7-year observational study

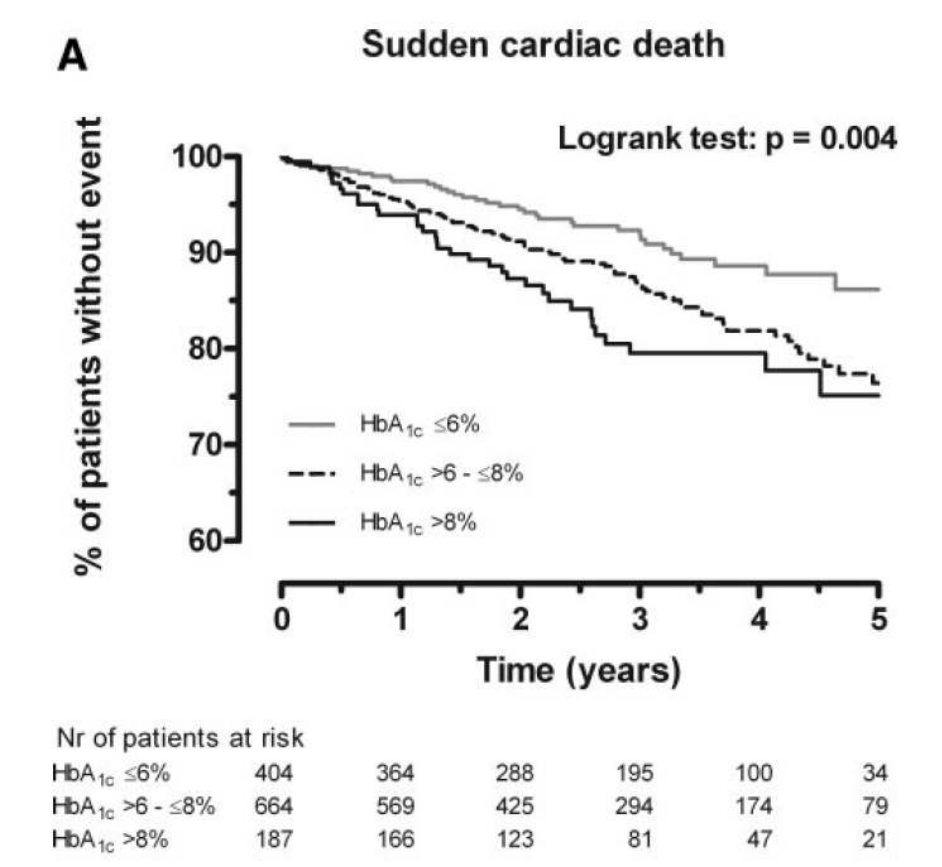


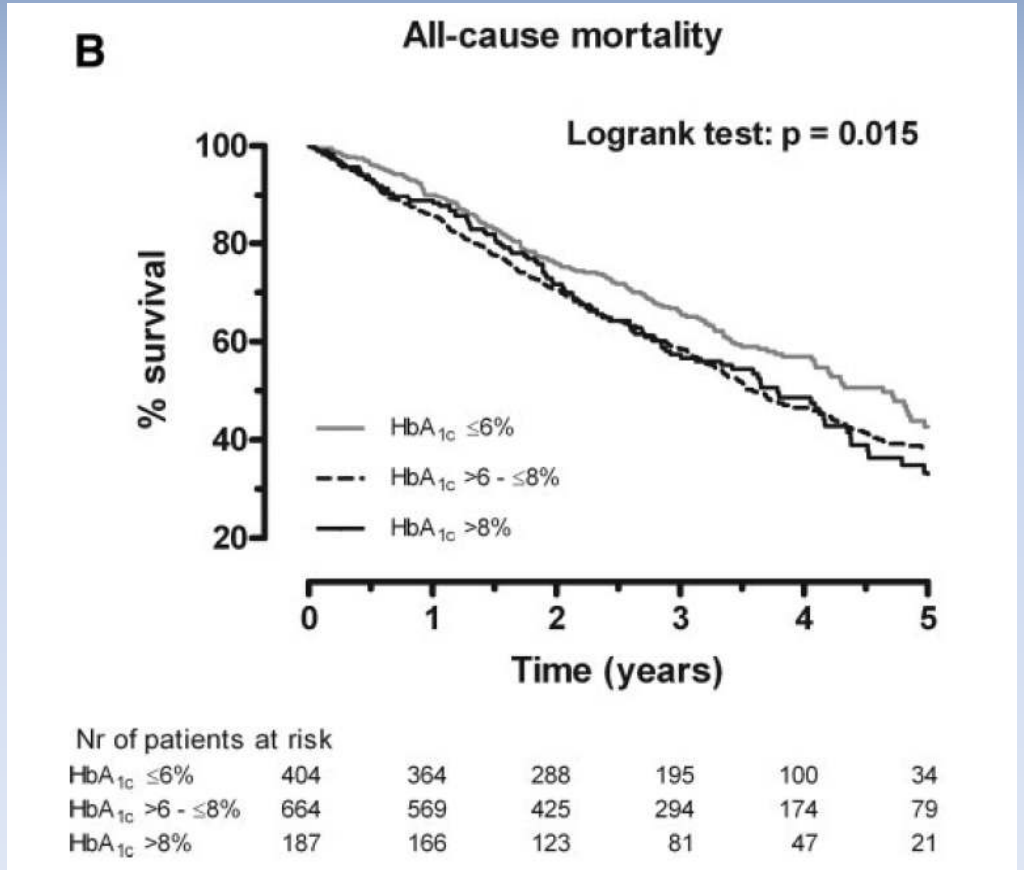
OR: poor A1C group (2.889, P=0.01), mean A1C (1.260 per 1%, p=0.003)

(Diabetes Care, 2006)

Impact of baseline glucose control on survival of diabetic patients on hemodialysis : Prospective observational study

- 4D (German Diabetes and Dialysis Study) study
- 1255 HD patients with type 2 DM
- Categorized by baseline HbA1C level





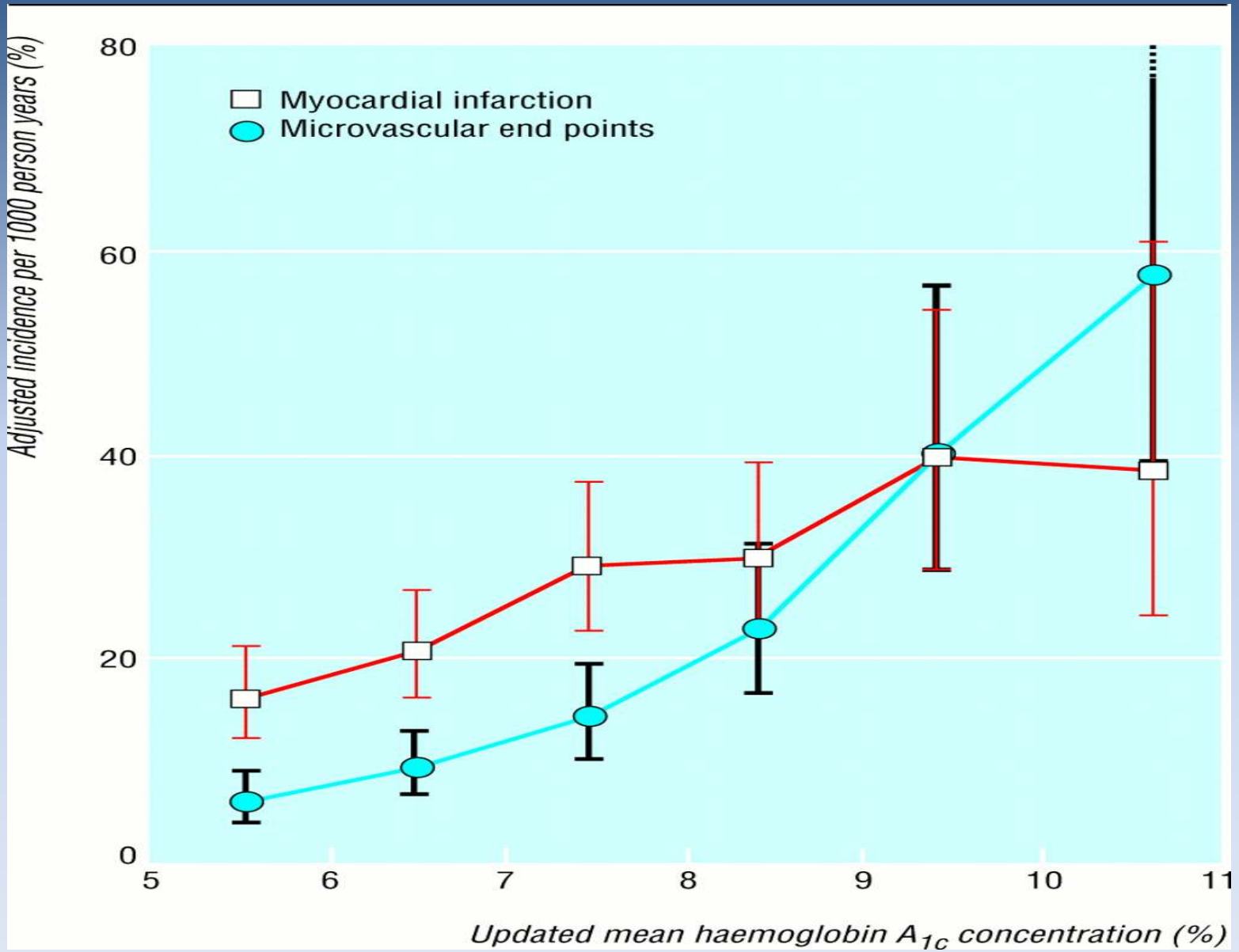
Impact of baseline glucose control on survival of diabetic patients on hemodialysis : Prospective observational study

Table 5. HRs and 95% CIs for All-Cause Mortality, Heart Failure Death, and Mortality Except for Sudden Cardiac Death According to Categories of HbA_{1c} at Baseline

	All-Cause Mortality		Heart Failure Death		Mortality Except for Sudden Death	
Model and HbA_{1c} Level	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Crude						
≤6	1		1		1	
>6–≤8	1.29 (1.07–1.55)	0.006	1.34 (0.65–2.75)	0.427	1.19 (0.97–1.47)	0.098
>8	1.31 (1.02–1.68)	0.033	1.44 (0.56–3.71)	0.452	1.10 (0.82–1.47)	0.543
Adjusted*						
≤6	1		1		1	
>6–≤8	1.34 (1.10–1.63)	0.004	1.53 (0.70–3.33)	0.288	1.19 (0.96–1.50)	0.117
>8	1.34 (1.02–1.76)	0.039	2.12 (0.75–5.98)	0.155	1.10 (0.80–1.52)	0.546

(Circulation, 2010)

UKPDS - follow up



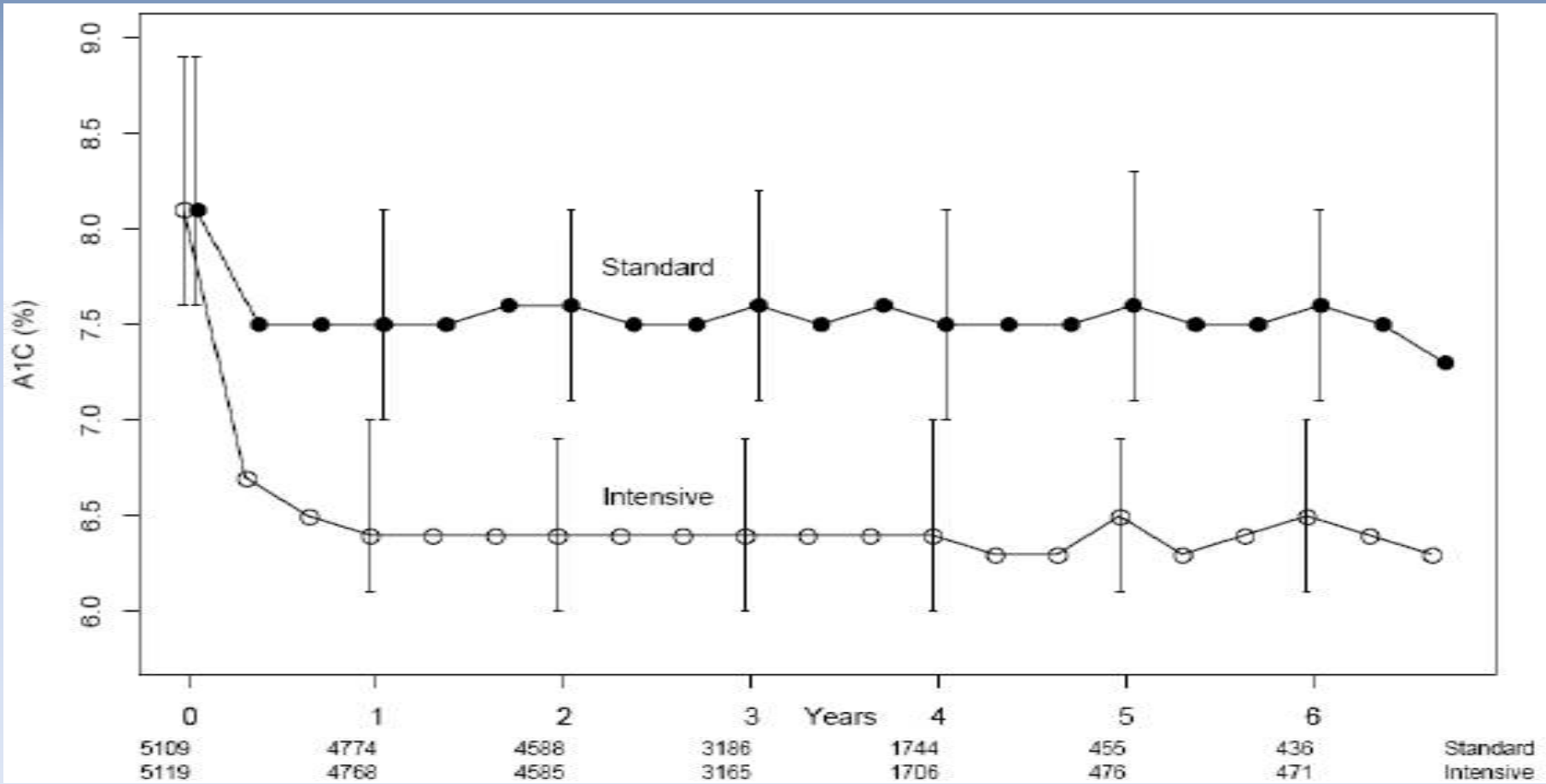
Stratton, BMJ 2000;321:405-412

ACCORD trial

10,251 patients (mean age, 62.2 years): median HbA1C level of 8.1%

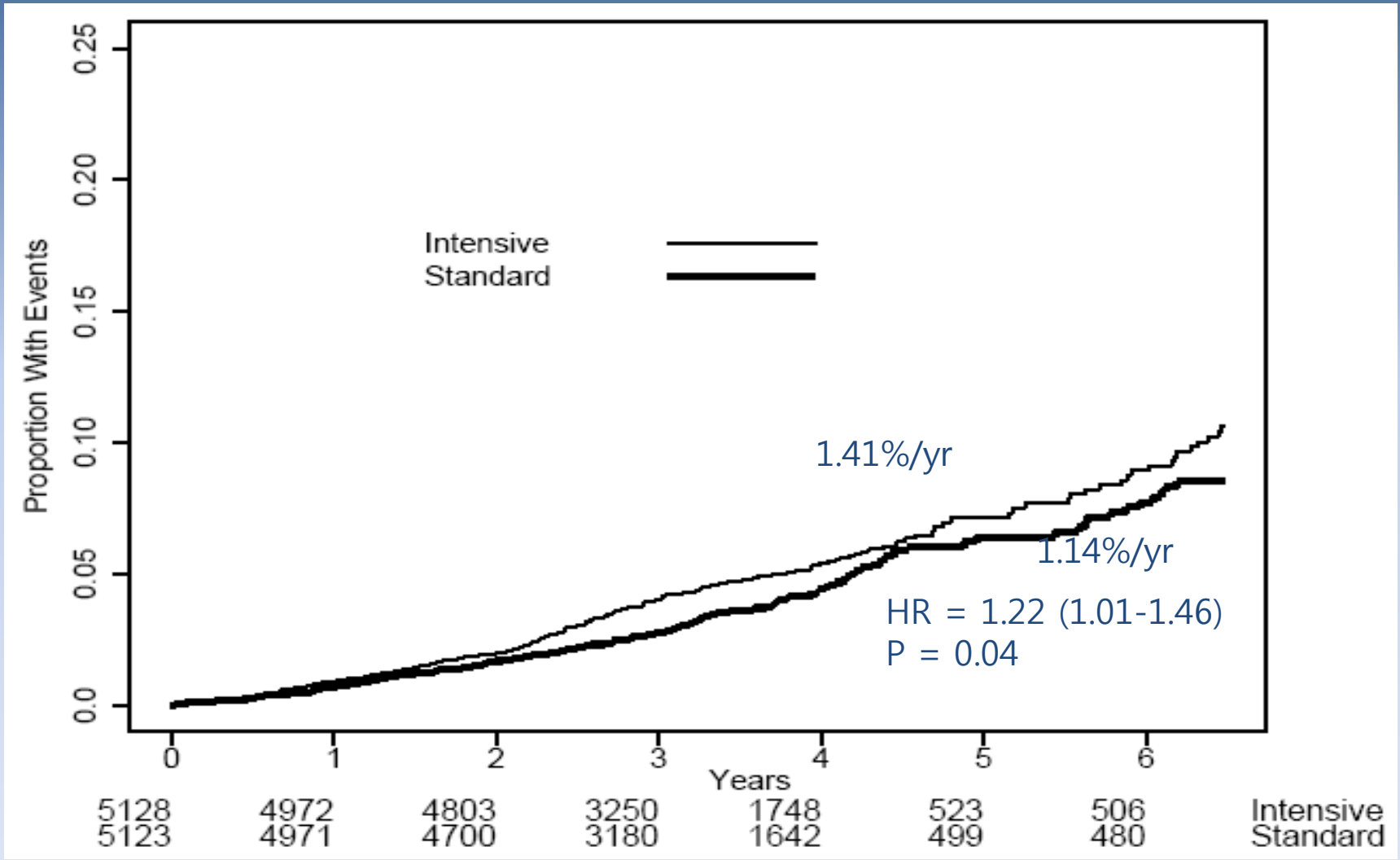
Intensive therapy (targeting HbA1C < 6.0%) or

standard therapy (targeting 7.0< HbA1C< 7.9%)



(New Engl J Med, 2008)

ACCORD trial



(New Engl J Med, 2008)

Table 3. Adverse Events, Clinical Measures, Tobacco Use, and Use of Nonglycemic Medication after Randomization.*

Variable	Intensive Therapy (N = 5128)	Standard Therapy (N = 5123)	P Value†
Adverse events			
Hypoglycemia — no. (%)			
Requiring medical assistance	538 (10.5)	179 (3.5)	<0.001
Requiring any assistance	830 (16.2)	261 (5.1)	<0.001
Fatal or nonfatal heart failure — no. (%)	152 (3.0)	124(2.4)	0.10
Motor vehicle accident in which patient was driver — no./total no. (%)	9/5033 (0.2)	14/5036 (0.3)	0.40
Any nonhypoglycemic serious adverse event — no. (%)	113 (2.2)	82 (1.6)	0.03
Fluid retention — no./total no. (%)‡	3541/5053 (70.1)	3378/5054 (66.8)	<0.001
Clinical measures			
Weight gain >10 kg since baseline — no./total no. (%)	1399/5036 (27.8)	713/5042 (14.1)	<0.001
Alanine aminotransferase >3 times ULN — no./total no. (%)§	51/5065 (1.0)	77/5061 (1.5)	0.02
Low-density lipoprotein cholesterol — mg/dl¶	90.8±33.5	90.6±34.0	0.74
Blood pressure — mm Hg¶			
Systolic	126.4±16.7	127.4±17.2	0.002
Diastolic	66.9±10.5	67.7±10.6	<0.001
Cigarette-smoking status — no. (%)‖			0.54
Current (previous 30 days)	505 (9.8)	508 (9.9)	
Former	2524 (49.2)	2467 (48.2)	
Never	2093 (40.9)	2143 (41.8)	
Missing data	6 (0.1)	5 (0.1)	
Use of nonglycemic medication — no./total no. (%)			
Antihypertensive	4664/5127 (91.0)	4714/5123 (92.0)	0.06
Angiotensin-converting–enzyme inhibitor	3512/5038 (69.7)	3621/5037 (71.9)	0.02
Aspirin	3736/4950 (75.5)	3753/4970 (75.5)	0.98
Beta-blocker	2395/5038 (47.5)	2450/5037 (48.6)	0.27
Statin	4432/5039 (88.0)	4425/5054 (87.6)	0.54

(New Engl J Med, 2008)

	ACCORD	ADVANCE	VADT
Participant characteristics			
n	10,251	11,140	1,791
Mean age (years)	62	66	60
Duration of diabetes (years)	10	8	11.5
Sex (% male/female)	39/61	42/58	97/3
History of CVD (%)	35	32	40
BMI (kg/m^2)	32	28	31
Median baseline A1C (%)	8.1	7.2	9.4
On insulin at baseline (%)	35	1.5	52
Protocol characteristics			
A1C goals (%) (I vs. S)*	<6.0 vs. 7.0–7.9	≤6.5 vs. "based on local guidelines"	<6.0 (action if >6.5) vs. planned separation of 1.5
Protocol for glycemic control (I vs. S)*	Multiple drugs in both arms	Multiple drugs added to gliclizide vs. multiple drugs with no gliclizide	Multiple drugs in both arms
Management of other risk factors	Embedded blood pressure and lipid trials	Embedded blood pressure trial	Protocol for intensive treatment in both arms
On-study characteristics			
Median duration of follow-up (years)	3.5 (terminated early)	5	5.6
Achieved median A1C (%) (I vs. S)*	6.4 vs. 7.5	6.3 vs. 7.0	6.9 vs. 8.5
On insulin at study end (%) (I vs. S)*	77 vs. 55*	40 vs. 24	89 vs. 74
On TZD at study end (%) (I vs. S)*	91 vs. 58*	17 vs. 11	53 vs. 42
On statin at study end (%) (I vs. S)*	88 vs. 88*	46 vs. 48	85 vs. 83
On aspirin at study end (%) (I vs. S)*	76 vs. 76*	57 vs. 55	88 vs. 86
Smokers at study end (%)	10	8	8
Mean blood pressure at study end (mmHg)			
Intensive glycemic control arm	126/67	136/74	127/68
Standard glycemic control arm	127/68	138/74	125/69
Weight changes (kg)			
Intensive glycemic control arm	+3.5	−0.1	+7.8
Standard glycemic control arm	+0.4	−1.0	+3.4
Severe hypoglycemia (participants with one or more episodes during study) (%)			
Intensive glycemic control arm	16.2	2.7	21.2
Standard glycemic control arm	5.1	1.5	9.9
Outcomes			
Definition of primary outcome	Nonfatal MI, nonfatal stroke, CVD death	Microvascular plus macrovascular (nonfatal MI, nonfatal stroke, CVD death) outcomes	Nonfatal MI, nonfatal stroke, CVD death, hospitalization for heart failure, revascularization
HR for primary outcome (95% CI)	0.90 (0.78–1.04)	0.9 (0.82–0.98); macrovascular 0.94 (0.84–1.06)	0.88 (0.74–1.05)
HR for mortality findings (95% CI)	1.22 (1.01–1.46)	0.93 (0.83–1.06)	1.07 (0.81–1.42)

*Medication rates for ACCORD are for any use during the study. I, intensive glycemic control; S, standard glycemic control; TZD, thiazolidinedione.

(Position statement of the ADA and scientific statement of the ACC, AHA, Diabetes Care, 2009)

Morbidity of hypoglycemia

- CNS : Coma/convulsions/transient brain damage/ intellectual impairment.
- CVS: Arrhythmia/MI/TIA/stroke.
- Eye: Vitreous haemorrhage
- Musculoskeletal: Fracture/accidental injury.

Risk factors for hypoglycemia

- Intensive insulin therapy & tight glycemic control.
- Hypoglycemia unawareness –acute & chronic.
- Long duration of diabetes.
- Increasing age.
- Excessive alcohol.
- Renal failure/ Hepatic failure
- Hypothyroidism/ Hypopituitarism/ Hypoadrenalism

Hypoglycemia in CKD patients

- 243,222 individuals in veterans health administration (VHA)

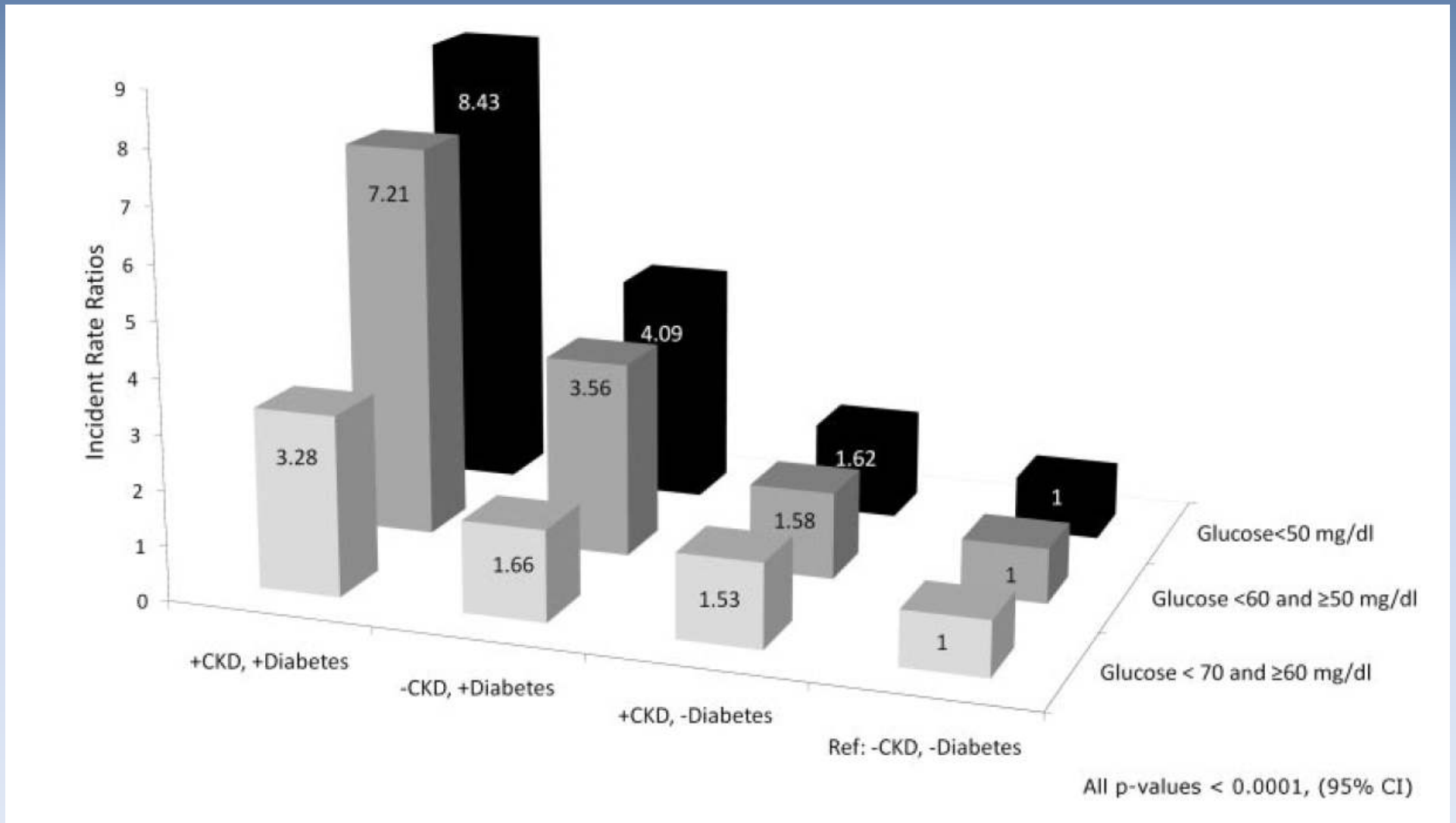
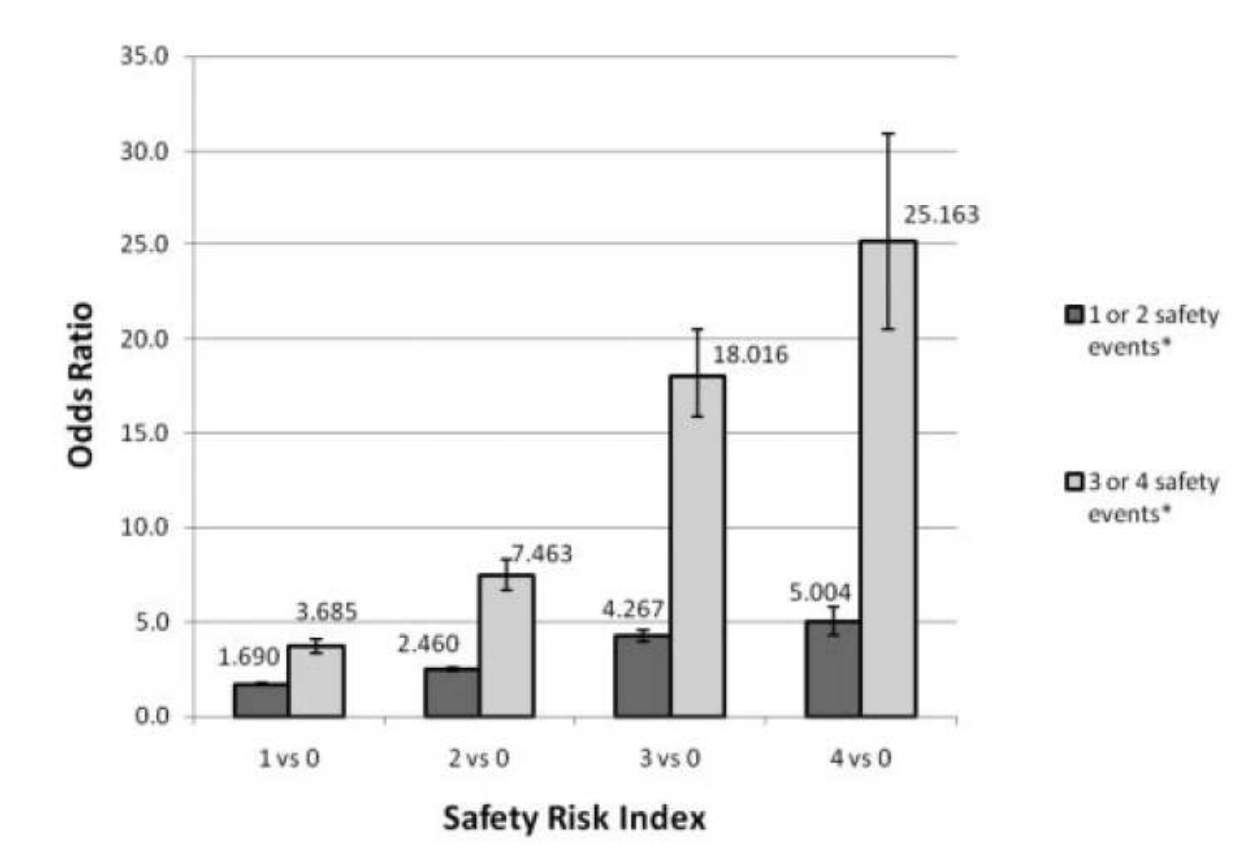


Table 3. Risk for death within 1 d of a hypoglycemia event, by glucose category and CKD

Parameter	Glucose ≥70 mg/dl (No Hypoglycemia)	Glucose <70 and ≥60 mg/dl	Glucose <60 and ≥50 mg/dl	Glucose <50 mg/dl
Inpatient				
no. of records	1,156,235	25,453	11,698	11,825
no CKD				
OR (95% CI)[a]	1.00 (reference)	2.54 (2.13 to 3.03)	3.79 (3.02 to 4.75)	9.95 (8.58 to 11.53)
no. of records	728,137	13,352	5652	5699
no. of death events[b]	2870 (0.4)	131 (1.0)	80 (1.4)	205 (3.6)
CKD				
OR (95% CI)[a]	1.12 (1.05 to 1.19)	1.85 (1.49 to 2.28)	4.10 (3.33 to 5.05)	6.09 (5.12 to 7.23)
no. of records	428,098	12,101	6046	6126
no. of death events[b]	2114 (0.5)	93 (0.8)	99 (1.6)	147 (2.4)
Outpatient				
no. of events	810,420	12,980	5870	5725
no CKD				
OR (95% CI)[a]	1.00 (reference)	4.34 (3.02 to 6.26)	7.36 (4.66 to 11.63)	13.28 (9.20 to 19.18)
no. of records	535,803	7328	2933	2679
no. of death events[b]	524 (0.1)	31 (0.4)	20 (0.7)	33 (1.2)
CKD				
OR (95% CI)[a]	1.09 (0.94 to 1.25)	3.98 (2.65 to 5.99)	3.28 (1.73 to 6.21)	6.84 (4.41 to 10.62)
no. of records	274,617	5652	2937	3046
no. of death events[b]	359 (0.1)	25 (0.4)	10 (0.3)	22 (0.7)

Adverse Safety Events in Chronic Kidney Disease: The Frequency of "Multiple Hits"

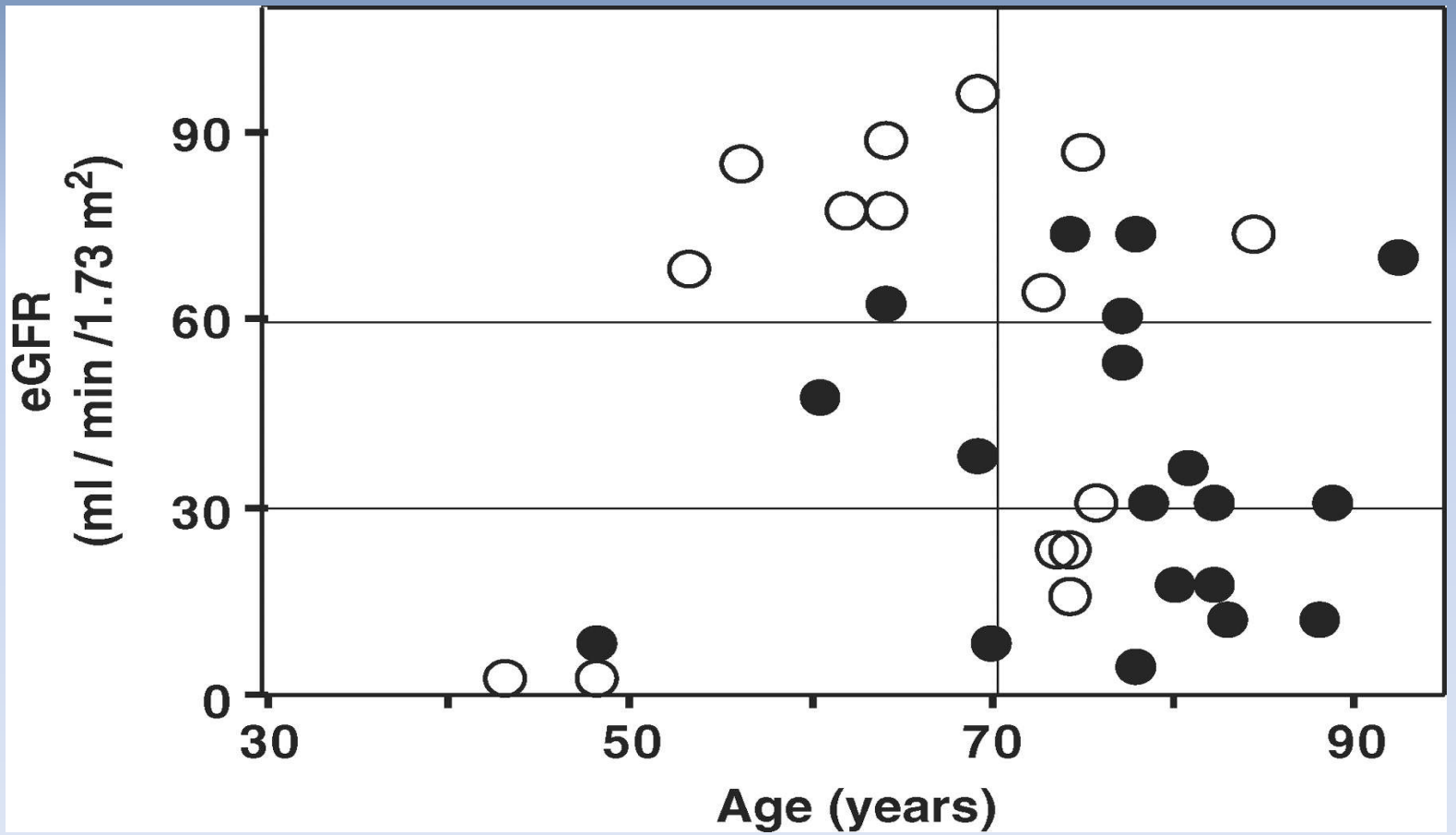
- 70,154 CKD individuals in veterans health administration (VHA)
- Safety indicator: hyperkalemia, hypoglycemia, PSI, incorrect dosing



(Clin JASN, 2010)

The consciousness disturbance due to severe hypoglycaemia in elderly subjects (>70) occurs frequently in subjects with CKD stages 3-5

Open circle indicates insulin-induced hypoglycaemia and
closed circle indicates sulfonylurea-induced hypoglycaemia.



(Nephrol Dial Transplant, 2009)

Standards of care proposed for elderly patients with diabetes and stages 3 to 4 CKD

No randomized controlled trials

Optimal glucose control on CVD is unsuccessful, may increase CV mortality

Parameter	Proposed
Glycosylated hemoglobin	<8.5%
BP	<140/90 mmHg
Hemoglobin	11.0 to 12.0 g/dl
Use of a diuretic	
Use of a β blocker (carvedilol, bisoprolol, and metoprolol)	(Unless contraindicated)
Use of low-dosage aspirin or antiaggregants	(Unless contraindicated)
Use of an ACEI	(Unless contraindicated)
Use of a statin	(Unless contraindicated)
Avoidance of calcium channel blockers verapamil, diltiazem, and nifedipine	

(Clin J Am Soc Nephrol, 2008)

Special Considerations in CKD Stages 3 to 5

Patients with decreased kidney function have increased risks for hypoglycemia

(1) decreased clearance of insulin and some of the oral agents used to treat diabetes

(2) impaired kidney gluconeogenesis

About one third of insulin degradation is carried out by the kidney, and impaired kidney function is associated with a prolonged half-life of insulin.

Thus, patients with type 1 diabetes receiving insulin who had significant creatinine elevations (mean, 2.2 mg/dL) had a 5-fold increase in the frequency of severe hypoglycemia.

Therefore, it is imperative that patients being treated intensively monitor their glucose levels closely and reduce doses of medicines (insulin and oral agents) as needed to avoid hypoglycemia.

Special Considerations in CKD Stages 3 to 5

First-generation sulfonylureas (eg, chlorpropamide, tolazamide, and tolbutamide) generally should be avoided in patients with CKD because these agents rely on the kidney to eliminate both the parent drug and active metabolites, resulting in increased half-lives and risk of hypoglycemia.

Of the second-generation sulfonylureas (eg, glipizide, gliclazide, glyburide, and glimepiride), glipizide and gliclazide are preferred agents because they do not have active metabolites and do not increase the risk of hypoglycemia in patients with CKD.

Metformin should not be given to patients with serum creatinine concentrations of 1.5 mg/dL or greater in men and 1.4 mg/dL or greater in women because it is cleared by the kidney and may build up with even modest impairment of kidney function, putting patients at risk of lactic acidosis.

Rosiglitazone is cleared by the liver and does not have to be reduced with impaired kidney function. Therefore, rosiglitazone does not increase the risk of hypoglycemia in patients with CKD, but it has the potential, along with pioglitazone, to worsen fluid retention.