What can be achieved with glycemic control?

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Michel Marre : conflicts of interest

Pharmas	*boards*	*lectures*	*scient. supports*
Abbott	yes	yes	no
Lilly	no	yes	no
MSD	yes	yes	yes
Novartis	no	no	yes
Novo-N	yes	yes	yes
Sanofi	yes	yes	yes
Servier	yes	yes	yes

Hyperglycemia/Microangiopathy: fatality, or consequence?

- **Siperstein MD, Unger RH, Madison LL: Studies of muscle capillary basement membrane in normal subjects, diabetic, and prediabetic patients. J Clin Invest, 1968**
- *…Finally, the discovery of thickened capillary basement membranes in prediabetic patients suggests that basement membrane hypertrophy is a relatively early lesion of the diabetic syndrome and provides further support for the conclusion* ***that this vascular defect is independent of carbohydrate derangements of diabetes mellitus***

Levels of Evidence
(Sir Austin Doyle, 1923)

- Case- Control Studies
- Prospective Follow-Up Studies
- Experimental Medicine
- Clinical Trials

III. — EXPLORATION PATHOLOGIQUE.

1° AUTOPSIE D'UN DIABÉTIQUE.

M. Cl. Bernard ayant eu l'occasion de faire l'autopsie d'un diabétique mort dans le service de M. Rayer, a pu mettre à profit les études qu'il a faites sur ce sujet, et donner à cette recherche une direction physiologique très propre à en caractériser les résultats. Une circonstance particulière est venue s'ajouter aux avantages que la science pouvait retirer de l'examen de ce cas : c'est que ce diabétique est mort subitement vers le troisième jour de son entrée à l'hôpital, et a pu par conséquent présenter à l'observation des faits qu'on ne rencontre pas dans les autopsies ordinaires des diabétiques qui s'éteignent lentement sous l'influence de leur maladie.

L'urine retirée au moyen de la sonde pendant que le sujet était encore chaud, contenait une grande quantité de sucre. Le foie déformé et beaucoup plus volu-

Comptes rendus des séances de la Société de Biologie et de ses filiales, 1850, tome 1, p. 80-81

mineux que dans l'état ordinaire en contenait en grande proportion. Les reins avaient également augmenté de volume ; dans l'état normal, le gauche pèse 141 grammes et le droit 125 ; sur ce diabétique, le rein gauche pesait 245 grammes et le droit 235. Le tissu du rein, préalablement lavé, a fourni du sucre, mais en beaucoup moins grande proportion que le foie. Le pancréas et la rate, diminués de volume, n'en contenaient point.

Les centres nerveux en étaient également privés.

Les liquides ont été soumis à l'analyse. Le sang contenait de grandes quantités de sucre dans tous les points où on l'a examiné. M. Cl. Bernard rappelle une autopsie dans laquelle le sérum du sang abandonné à lui-même était devenu acide par suite de la destruction du sucre. Cette observation s'appuie sur une circonstance de cette dernière autopsie : c'est qu'on a trouvé du sucre dans de la sérosité qui remplissait le péricarde. Or cette même sérosité, alcaline au moment où on l'a retirée du péricarde, est devenue acide par suite de la destruction du sucre.

Le suc intestinal et le suc gastrique, qui sont très-propres à favoriser cette destruction, n'en contenaient pas. (M. Cl. Bernard observe qu'il a rencontré du sucre dans le sperme d'un chien qu'il avait artificiellement rendu diabétique.)

Cette dernière autopsie montre donc que, dans les cas où l'on peut étudier les tissus et les liquides d'un diabétique que la mort enlève subitement, on peut rencontrer du sucre dans le sang, dans le foie et dans les reins.

Quant aux différences de réactions offertes par les liquides et rapportées jusqu'ici à la cause qui produit le diabète, on voit qu'elles dépendent simplement du mode de destruction du sucre.

Comptes rendus des séances de la Société de Biologie et de ses filiales, 1850, tome 1, p. 80-81

Diabète et complications dégénératives
Présentation d'une étude prospective portant sur 4400 cas observés entre 1947 et 1973 (Première partie*)

J. Pirart – ***Diabète & Métabolisme, 1977 Jun;3(2):97-107***

L'incidence et la prévalence de la neuropathie et de la microangiopathie (rétinienne et rénale) et, à un moindre degré, celles de la macroangiopathie (coronaire et périphérique) sont fonction de la durée connue du diabète. Pour cette raison, toutes les corrélations étudiées ultérieurement ont tenu compte du facteur durée.

L'âge en soi n'a pas d'influence sur les éléments de la triopathie alors qu'il augmente fortement le risque d'athérosclérose (prévalence et incidence).

L'obésité actuelle (en soi) n'influence aucune des cinq complications étudiées dans cette vaste série de diabétiques.

L'incidence annuelle de neuropathie, rétinopathie et néphropathie est nettement liée au degré de contrôle de chaque année, quel que soit le passé glycémique du patient.

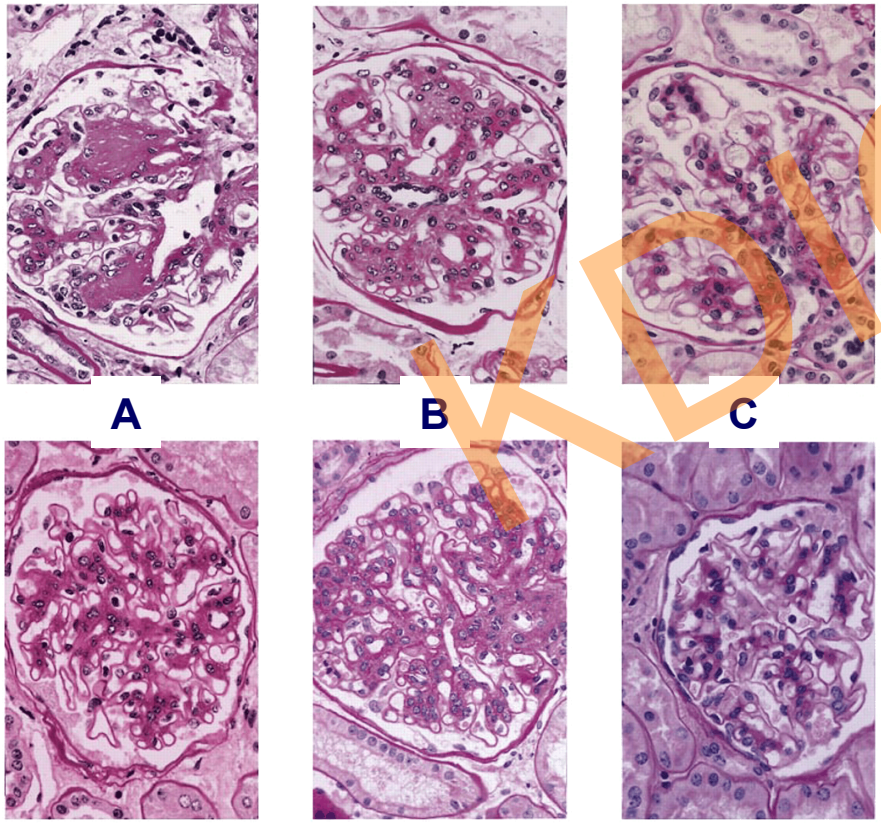
La prévalence et l'incidence des deux manifestations d'athérosclérose semblent sans relation avec le degré de contrôle glycémique.

Experimental Medicine

- SM Mauer, MW Steffes, AF Michael, DM Brown: Studies of Diabetic Nephropathy in Animals and Man, Diabetes, 1976, 35(suppl 2): 850-857

Reversal of Lesions of Diabetic Nephropathy after Pancreas Transplantation

Paola Fioretto, M.D., Ph.D., Michael W. Steffes, M.D., Ph.D., David E.R. Sutherland, M.D., Ph.D., Frederick C. Goetz, M.D., and Michael Mauer, M.D., NEJM, 1998

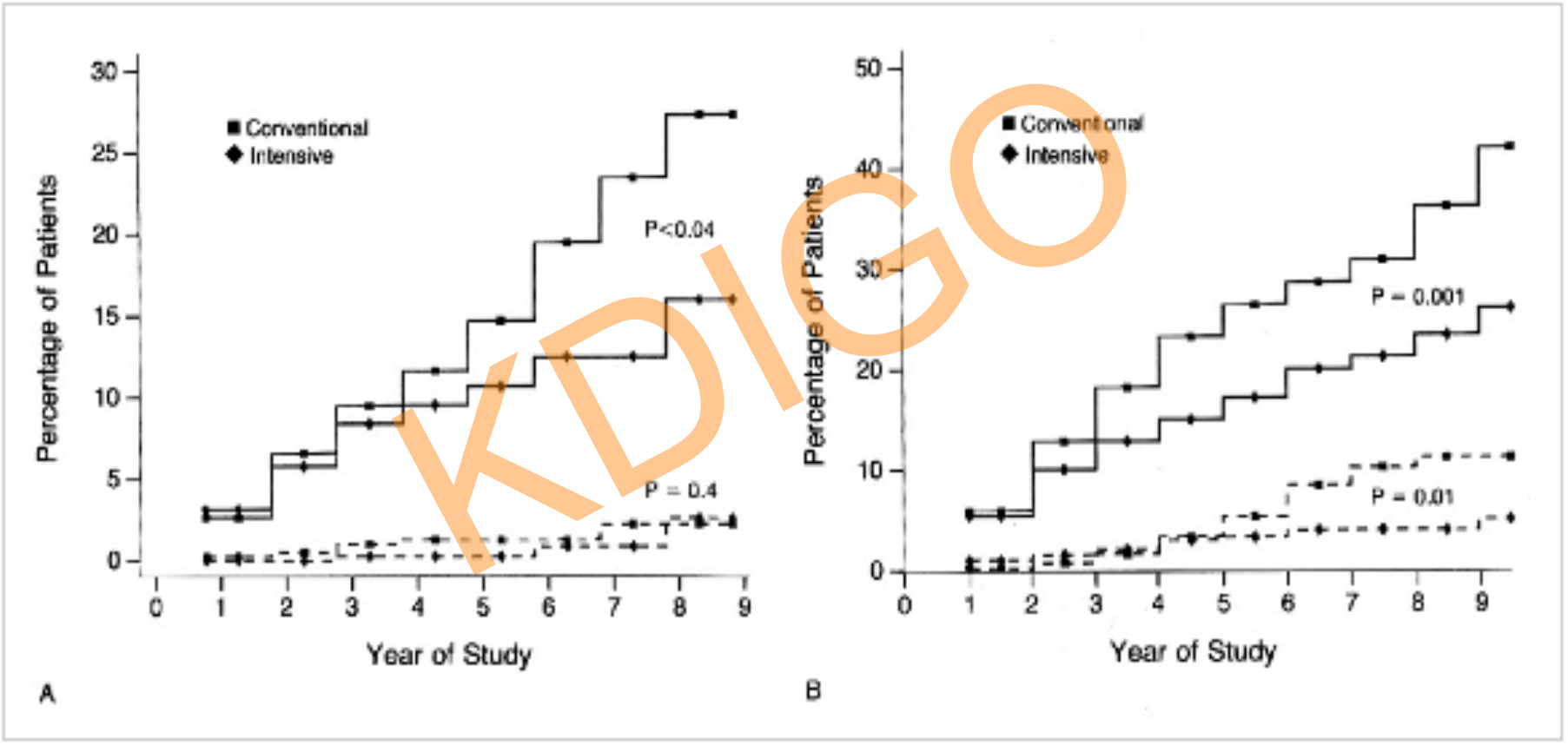


Photomicrographs of Renal-Biopsy Specimens Obtained before and after Pancreas Transplantation from a 33-Year-Old Woman with Type 1 Diabetes of 17 Years' Duration at the Time of Transplantation (Periodic Acid–Schiff, x120).

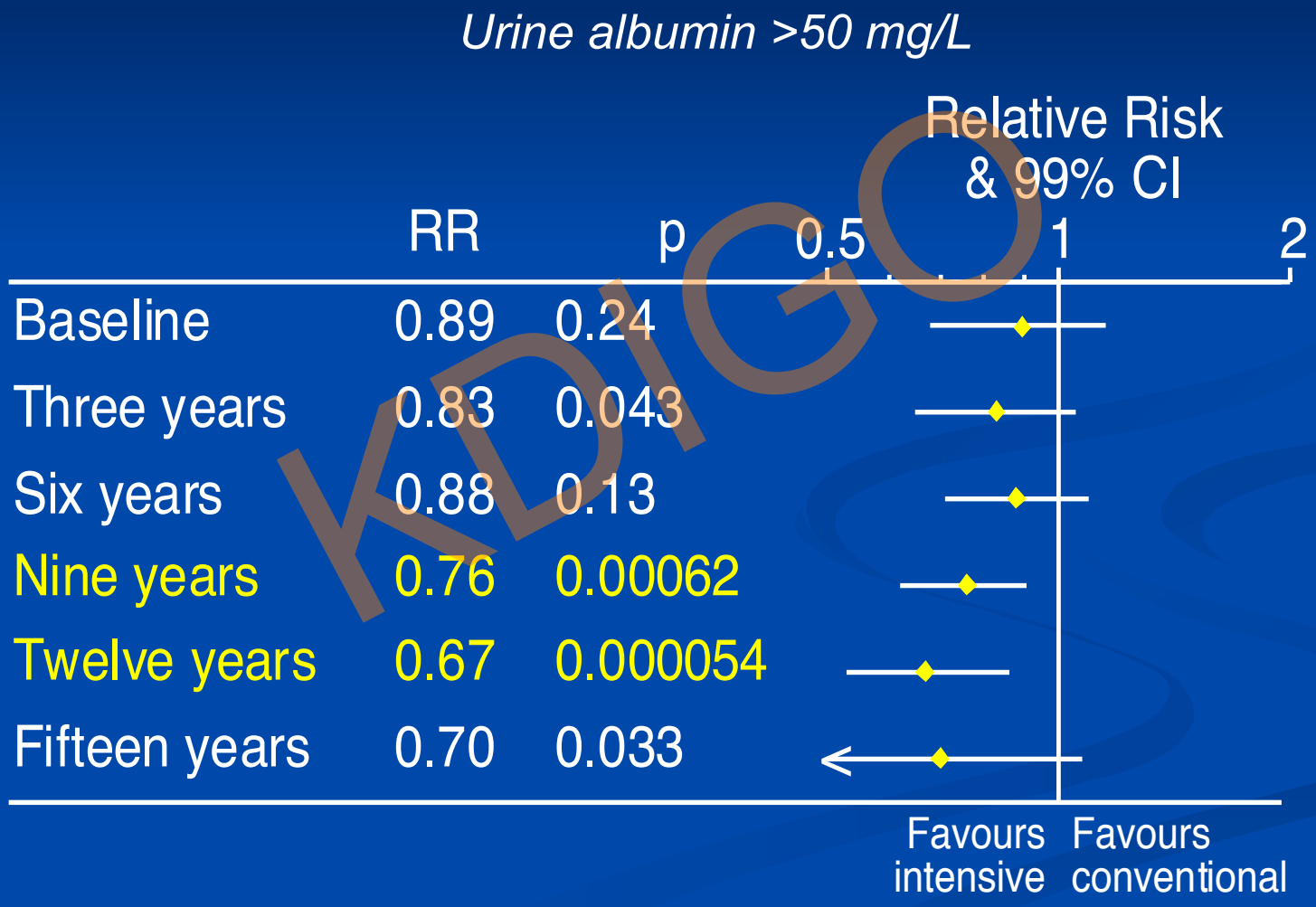
A = Baseline
B = 5 years after Tx
C = 10 years after Tx

Photomicrographs of Renal-Biopsy Specimens Obtained before and after Pancreas Transplantation from a 31-Year-Old Woman with Type 1 Diabetes of 27 Years' Duration at the Time of Transplantation (Periodic Acid–Schiff, x120).

DCCT, 1993, primary vs secondary interventions



UKPDS : Microalbuminuria onset



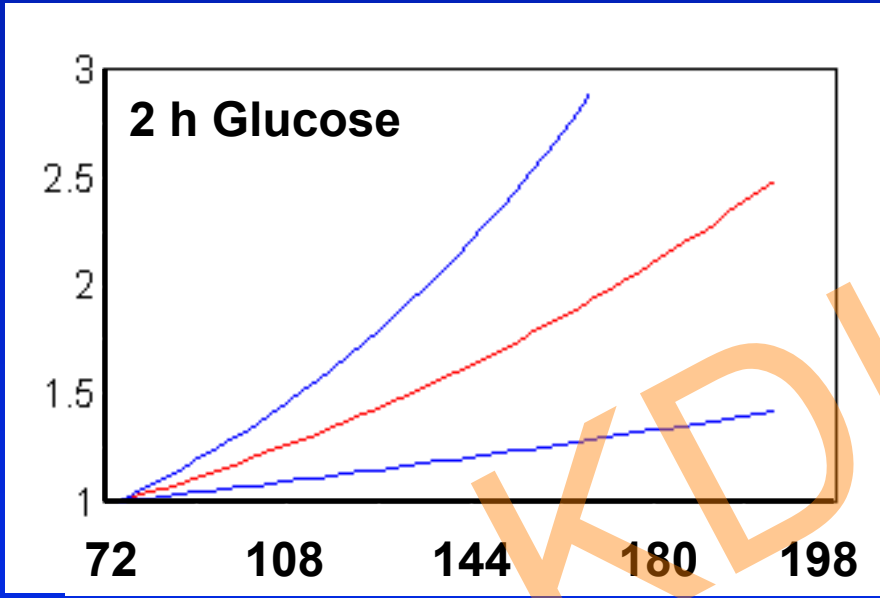
Strict glycemic control:

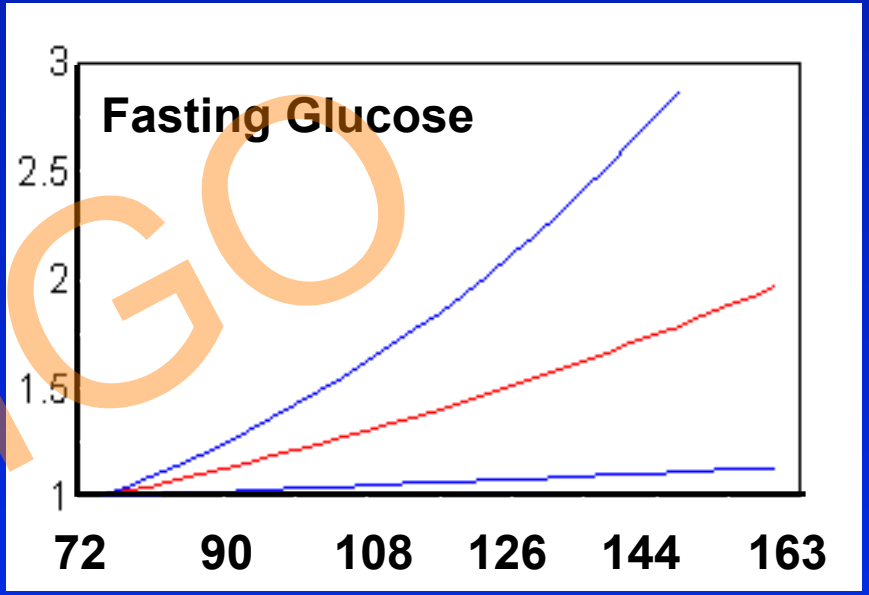
- Strict glycemic control beneficial for *microcirculation, and/or large circulation?*
- *Which level* of glycemic control?
- From *which stages* of diabetes/kidney disease?
- Differences between *T1DM and T2DM?*
- *Interaction/additive effects with other interventions* (e.g, BP control)?
- Which side effects (*hypoglycemias, weight gain*)?
- Which *drugs*?

Strict glycemic control beneficial for microcirculation, and/or large circulation?

- ***Association vs causation***

G & CV Events: Meta-Regression





NB: 2 h G=140: RR=1.58 (1.19-2.10) **Fasting G=110: RR=1.33 (1.06-1.67)**

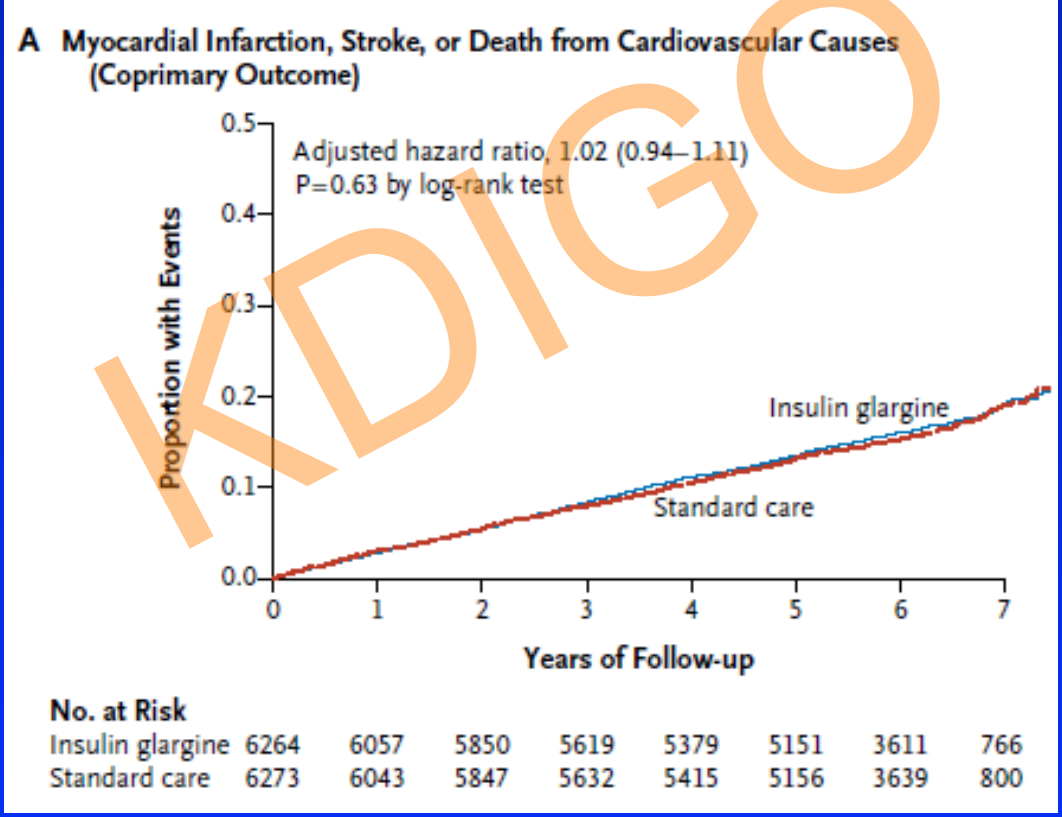
After remove any DM: *P* = 0.0006 for 2 h G
***P* = 0.06 for FPG**

Coutinho M, Gerstein HC et al. *Diabetes Care.* 1999;22:233-240.

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators

N Engl J Med 2012; 367:319-328



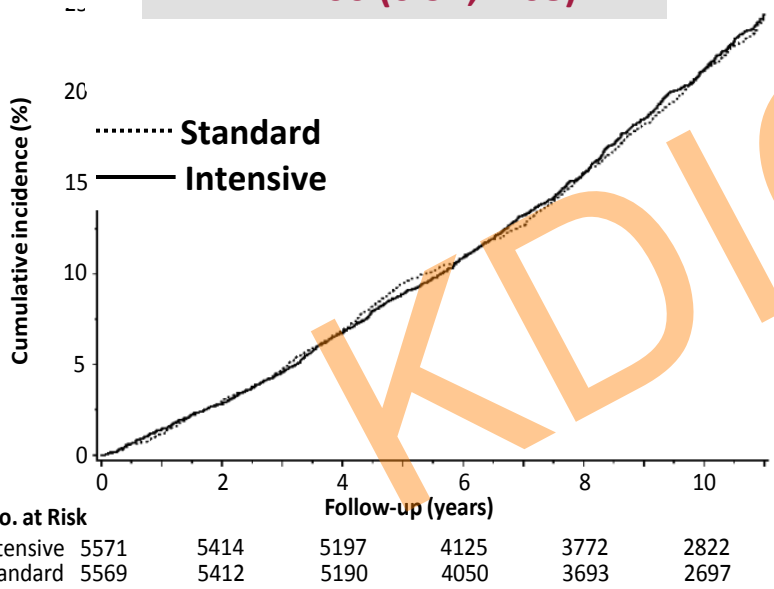
In total : **CONTROL** *(Diabetologia, 2009)*

- **UKPDS+ACCORD+ADVANCE+VADT over 4 years =**
- major CV events HR 0.91 (95%CI 0.84-0.99)
- Non-fatal MI HR 0.85 (95%CI 0.76-0.94)
- All-cause mortality HR 1.04 (95%CI 0.90-1.20)
- CV death HR 1.10 (95%CI 0.84-1.42)

Mortality
(overall in-trial and post-trial follow-up)

Death from any cause

HR 1.00 (0.92, 1.08)

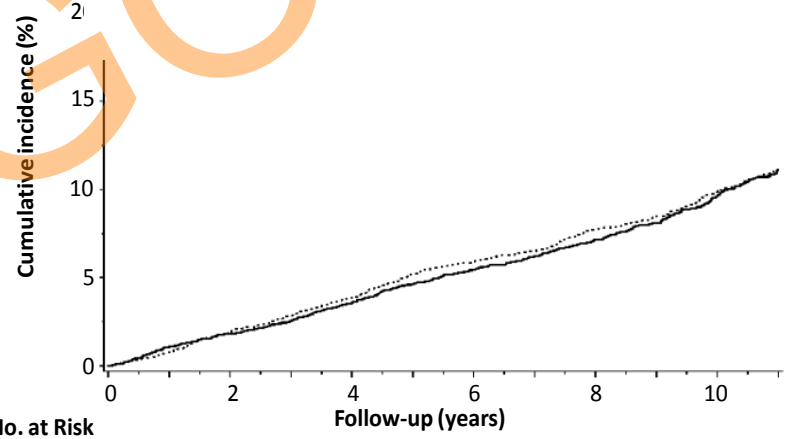


No. at Risk

Intensive	5571	5414	5197	4125	3772	2822
Standard	5569	5412	5190	4050	3693	2697

Cardiovascular death

HR 0.97 (0.86, 1.10)

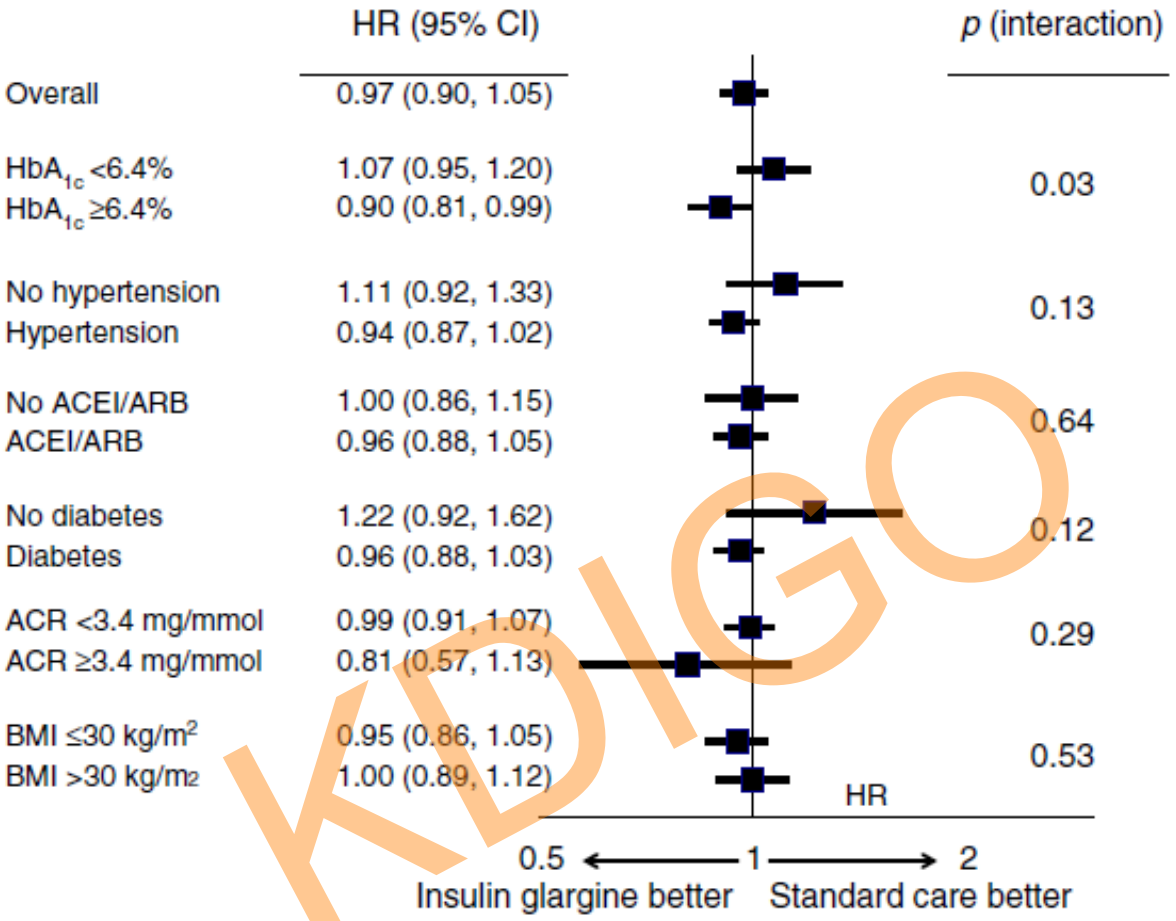


No. at Risk

Intensive	5571	5402	5188	4125	3772	2822
Standard	5569	5399	5179	4050	3693	2697

Follow-up (years)

Which Level of Glycemic Control?



Basal insulin glargine and microvascular outcomes in dysglycaemic individuals: results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial

Diabetologia (2014) 57:1325-1331

Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. **S Zoungas et al (ADVANCE collaborative Group), Diabetologia, 2012, 55:636-43**

... Within the range of HbA1c studied (5.5 – 10.5%), there was evidence or « thresholds », such that below HbA1c levels of 7.0% for macrovascular events and death, and 6.5% for microvascular events, there was no significant change in risks (all p>0.8) ...

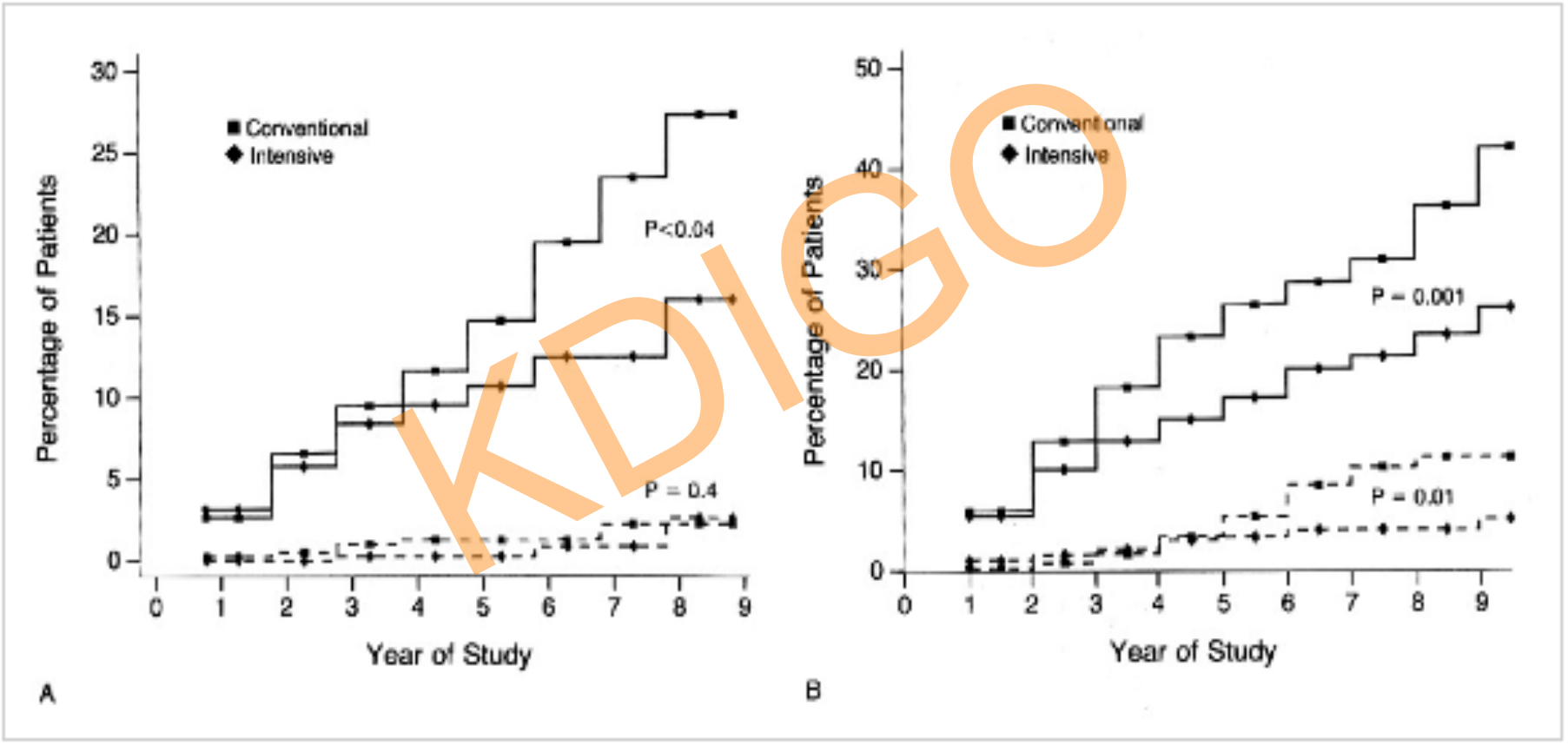
Which level of glycemic control?

- May be different or micro- and for large circulation
- Unexpected results…
- But microcirculation status conditions target organs of CV diseases

From which stages of diabetic kidney disease?

- Diabetes Duration and Complications
- Which renal outcome? Increased UAE vs reduced GFR
- Interest for retinal disease

DCCT, 1993, primary vs secondary interventions



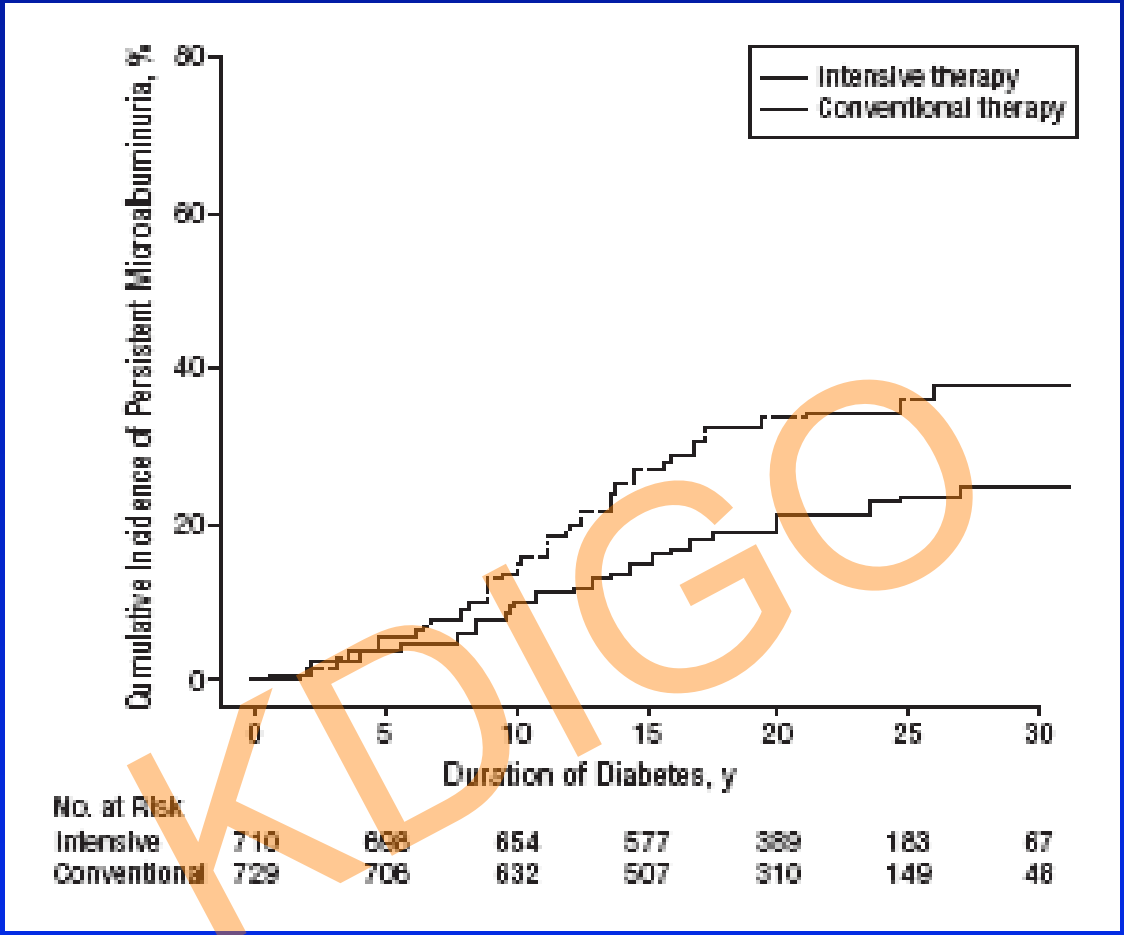


Figure 1. Cumulative incidence of persistent microalbuminuria in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study by duration of type 1 diabetes and by Diabetes Control and Complications Trial treatment assignment. I de Boer et al, Arch Int Med, 2011

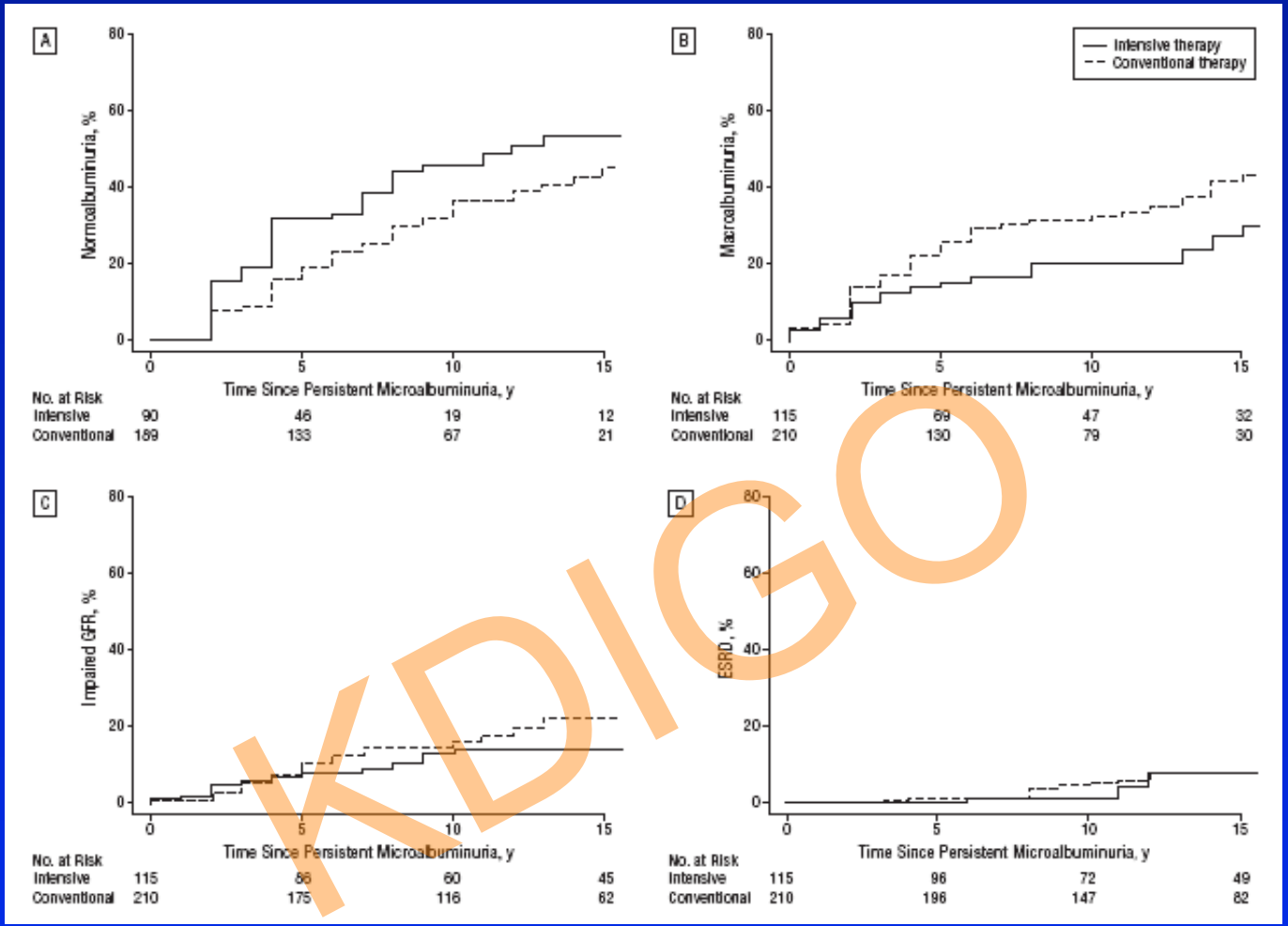
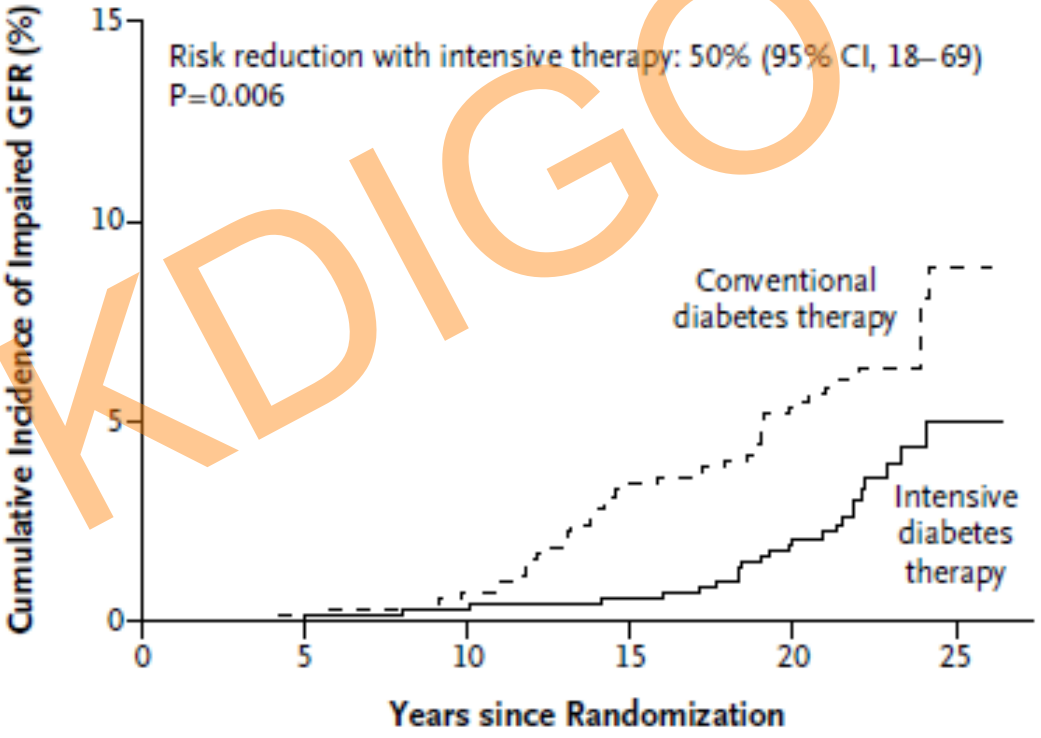


Figure 4. Cumulative incidence of long-term renal outcomes after the development of persistent microalbuminuria (time 0) among 325 participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study by Diabetes Control and Complications Trial treatment assignment. A, Regression to normoalbuminuria. B, Progression to macroalbuminuria. C, Impaired glomerular filtration rate (GFR). D, End-stage renal disease (ESRD). I de Boer et al, Arch Int Med, 2011, 171: 412-420

Memory effects during DCCT/EDIC: impaired GFR

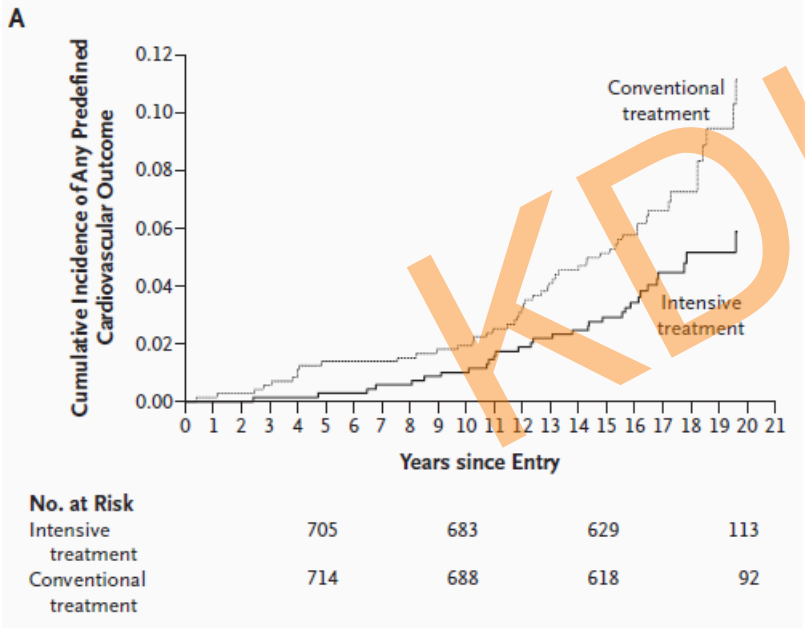
- *N Engl J Med 2011;365:2366-76.*

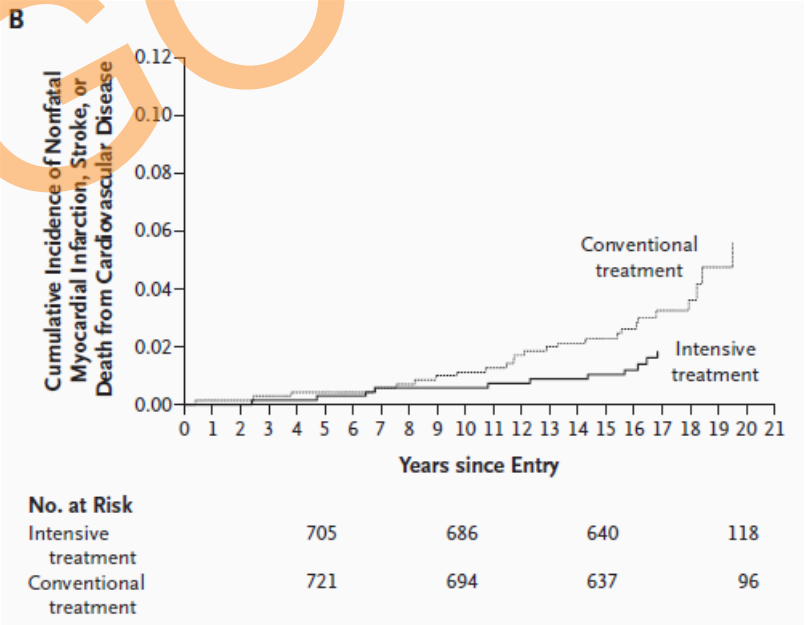


No. at Risk						
Intensive therapy	711	704	684	672	619	108
Conventional therapy	730	719	697	657	594	90

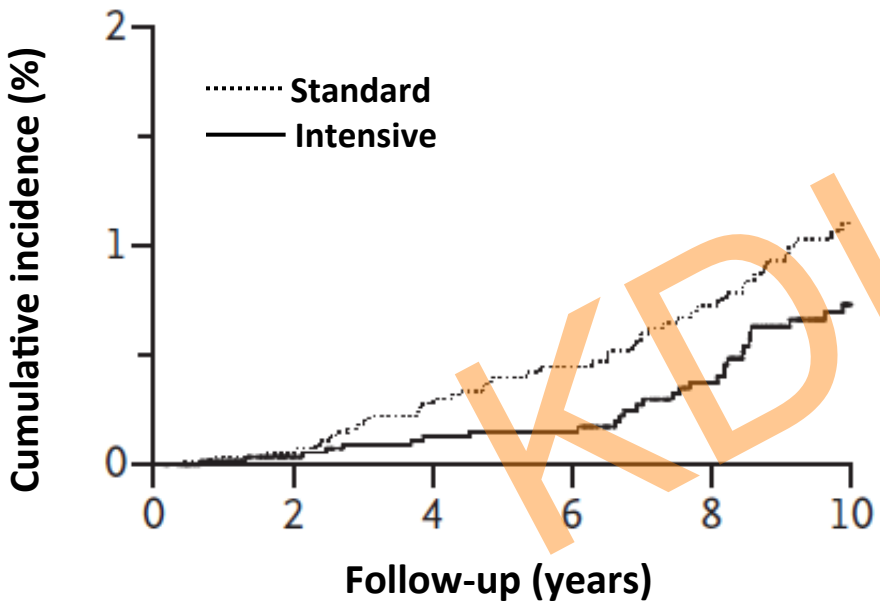
Memory effects during DCCT/EDIC: CV events

- *N Engl J Med 2005;353:2643-53.*





End-stage kidney disease (overall in-trial and post-trial follow-up)



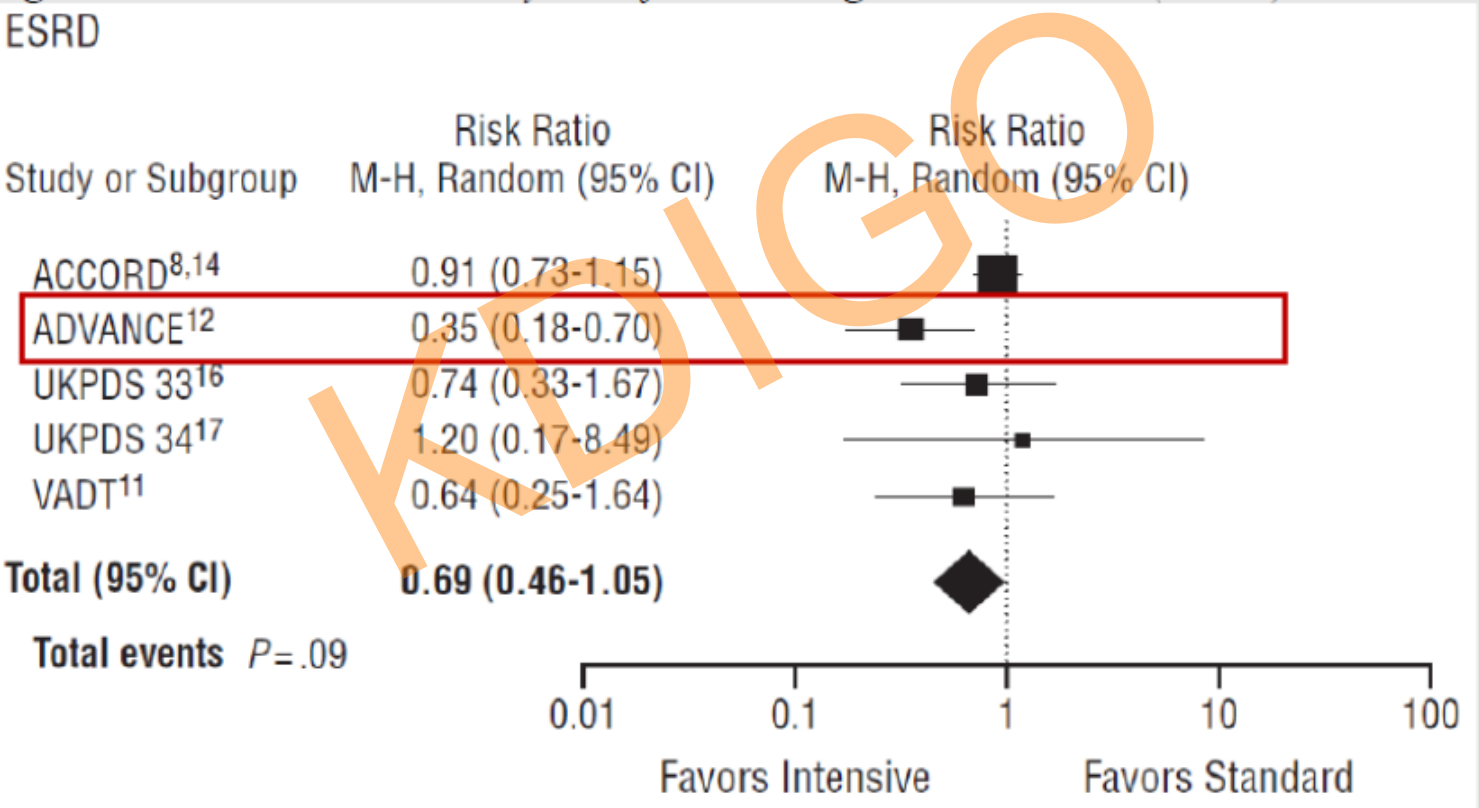
	In-trial (5.0 yrs)	Post-trial (5.4 yrs)	Overall (9.9 years)
End-stage kidney disease			
HR (95%CI)	0.35 (0.15-0.83)	0.65 (0.38-1.11)	0.54 (0.34-0.85)
Event no. (intensive vs standard)	(7 vs 20) **-13**	(22 vs 33) **-11**	(29 vs 53) **-24**

Relative risk reduction 46%
95% CI: 15 to 66%
p<0.01

Role of Intensive Glucose Control in Development of Renal End Points in Type 2 Diabetes Mellitus

Systematic Review and Meta-analysis

Figure 1: Pooled risk ratios by trial for end-stage renal disease (ESRD).

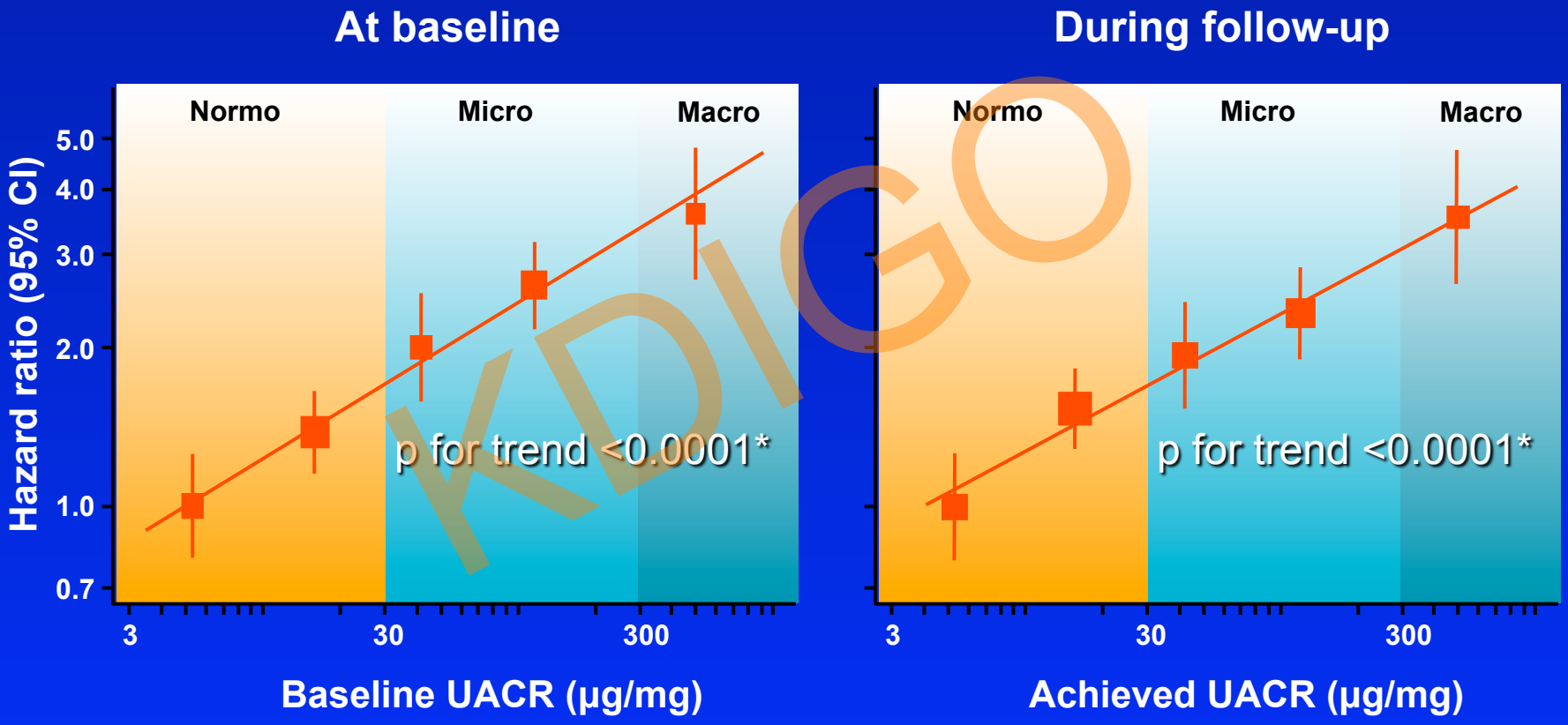


Arch int Med 2012;172(10)761-9

Which marker for kidney involvement? Increased UAE, or reduced GFR?

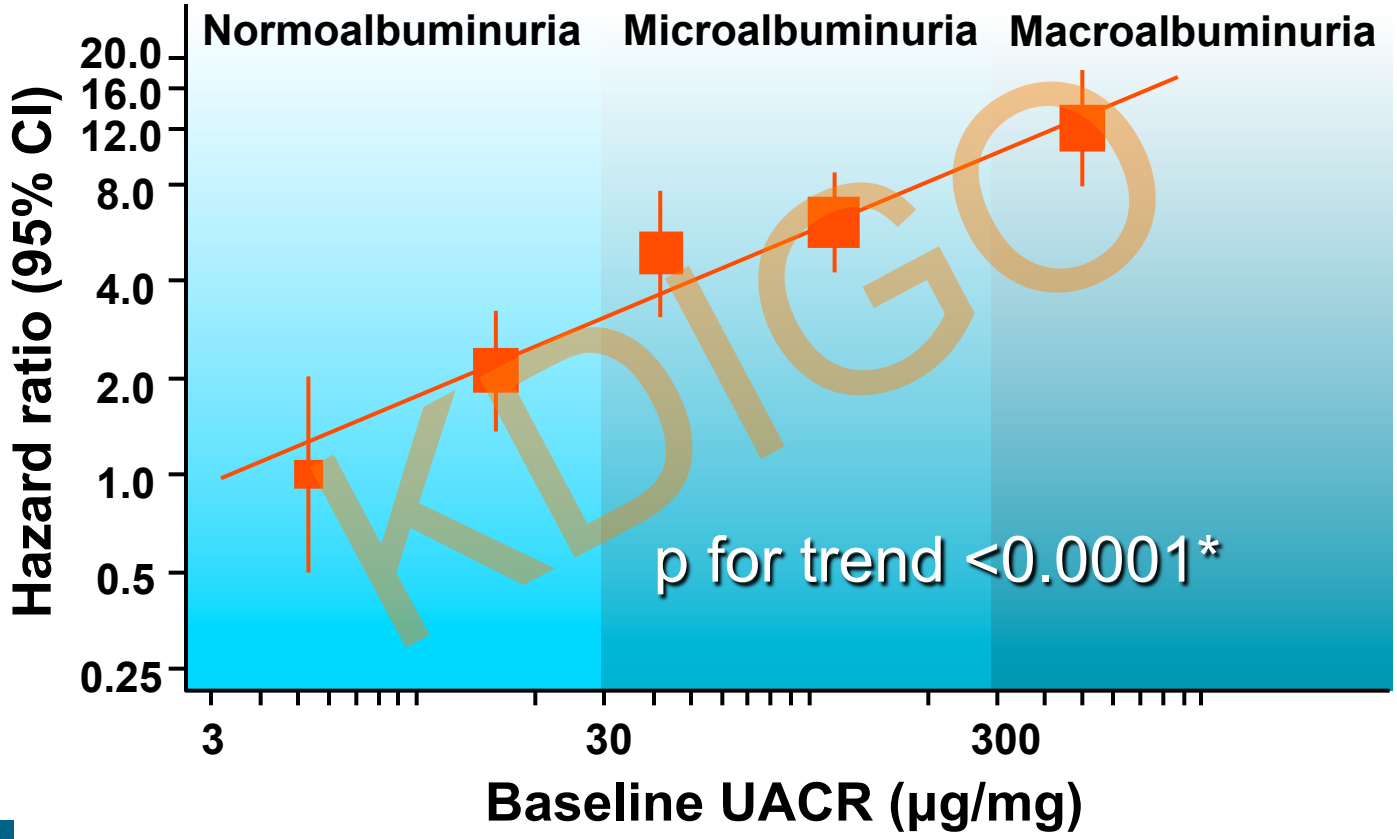
- **Predictive value of microalbuminuria:**
- -IDDM (type 1): Viberti et al (1982), Mathiesen et al (1983), Mogensen et al (1984)
- -NIDDM (type 2): Mogensen (1984), Viberti et al (1985): premature (CV) mortality >>renal death
- **Deleting µalb from our catalogue:** analogy with Cardiologists deleting ***LVH*** from their strategies
- **µAlb, a modifiable biomarker**

Risk of CV death by albuminuria at baseline and achieved during follow-up in ADVANCE



**Adjusted for age, sex, HbA_{1c}, serum lipids, BMI, smoking, alcohol use, and study drug*

Risks of ESRD or creatinine doubling >200 µmol/l by baseline albuminuria in ADVANCE

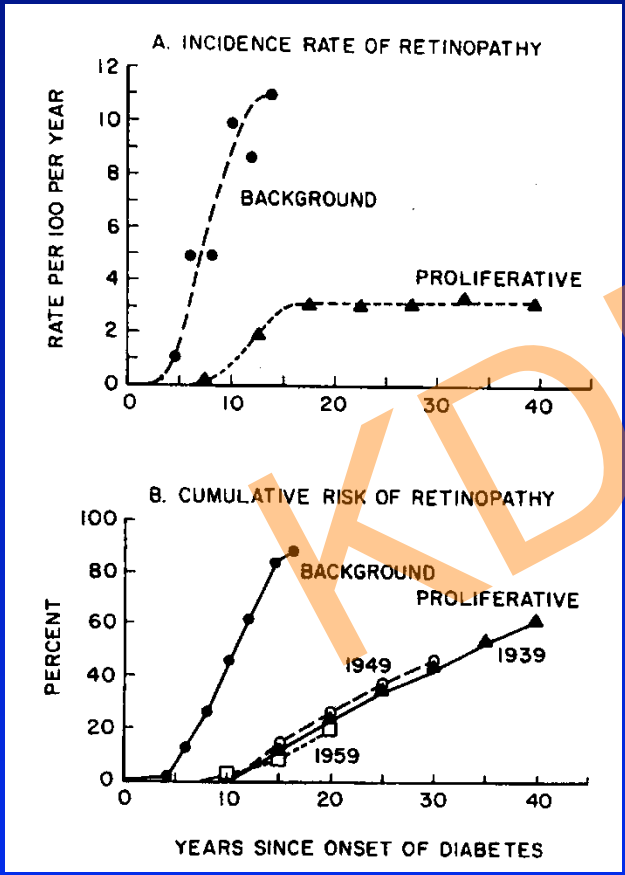


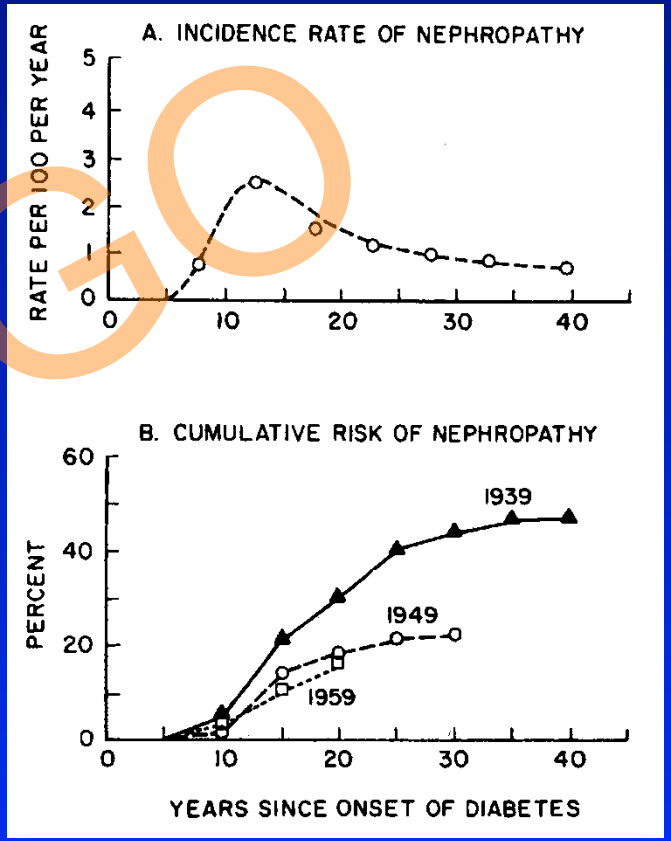
*Adjusted for age, sex, HbA_{1c}, serum lipids, BMI, smoking, alcohol use, and study drug

Interest in retinal disease: a marker for microvacular disease due to hyperglycemia

Not all diabetic patients susceptible to kidney disease

Historical, prospective, follow-up of type1 diabetic patients in specialized clinics



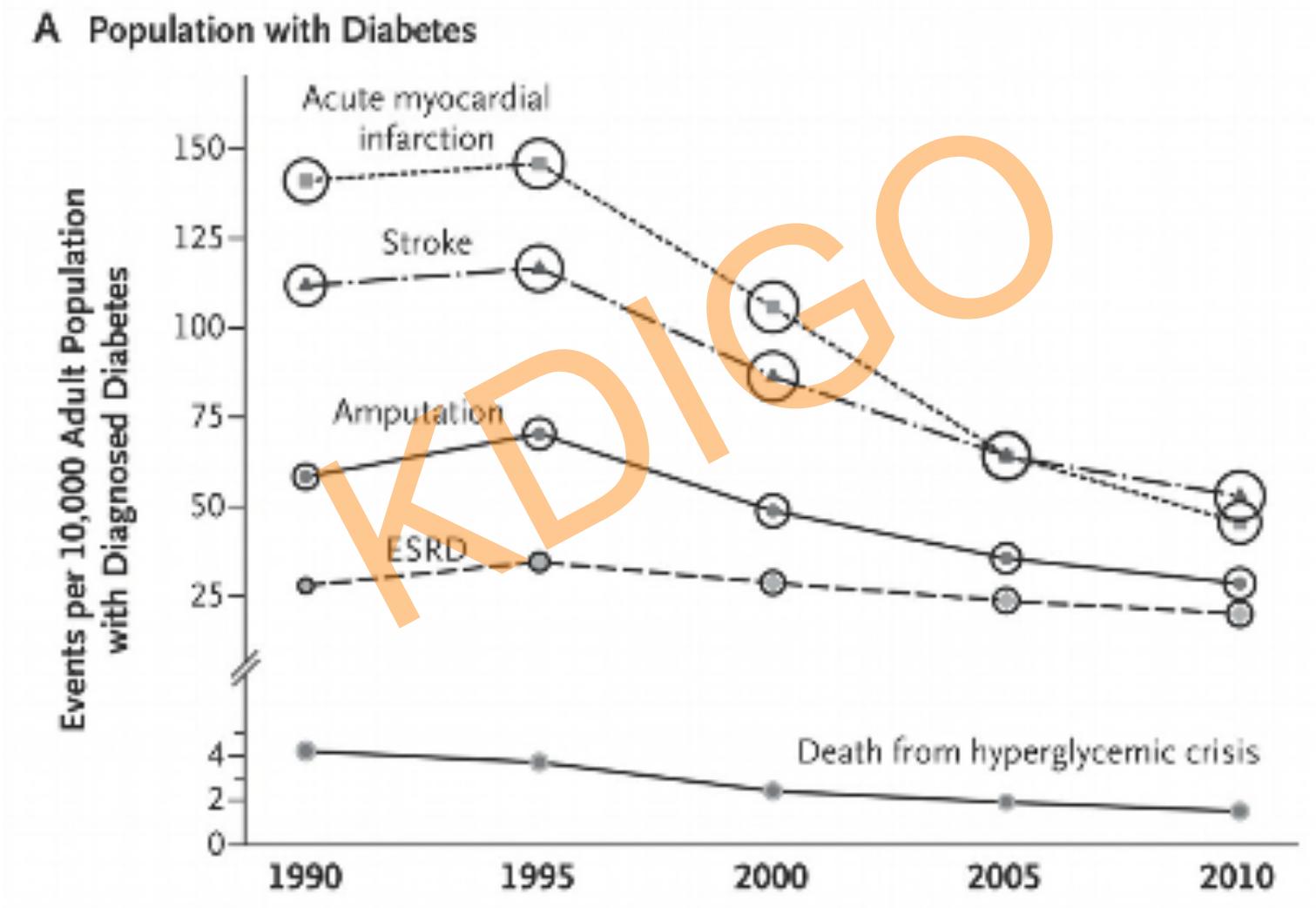


Krolewski A.J. et al, N. Engl. J. Med., 1987, 22: 1391-1398

Differences of risks for kidney disease between T1DM and T2DM

- Uncertainty regarding causes for diabetes
- T2DM onset at earlier age
- T2DM combine CV and µvascular risks
- Increased life expectancy
- => intensive glucose strategies tested in T1DM applicable to « intermediate » diabetes

Complications in the 2010s: *(NEJM, 2014)*

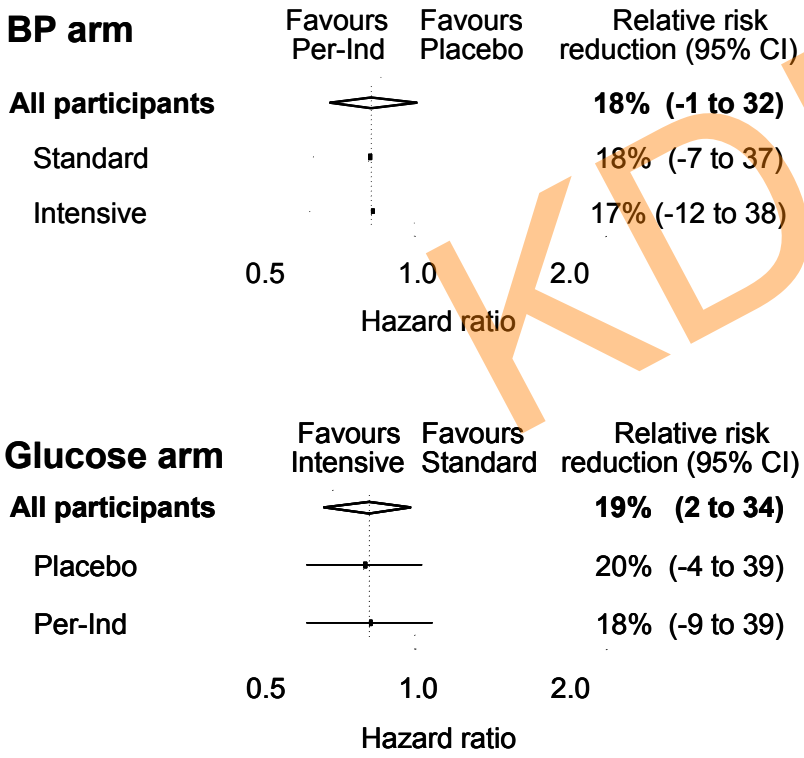


Interaction with other interventions (BP control)

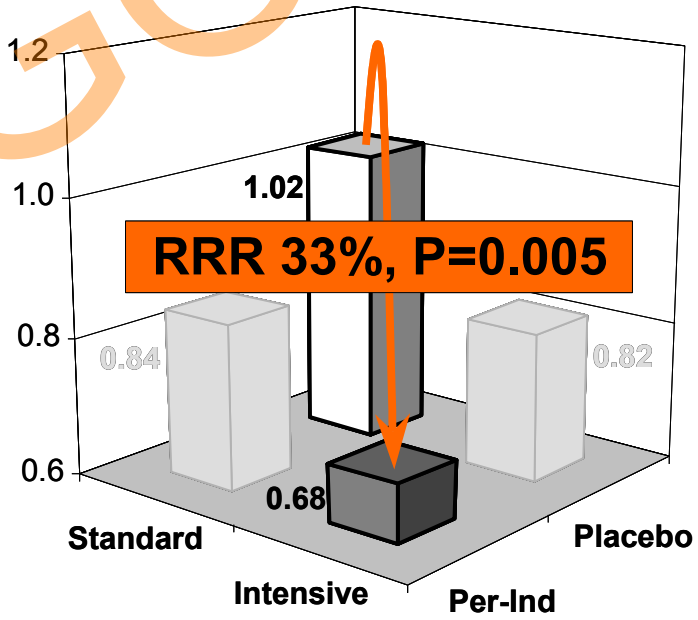
ADVANCE

New or worsening nephropathy

Hazard ratios



Annual event rate %

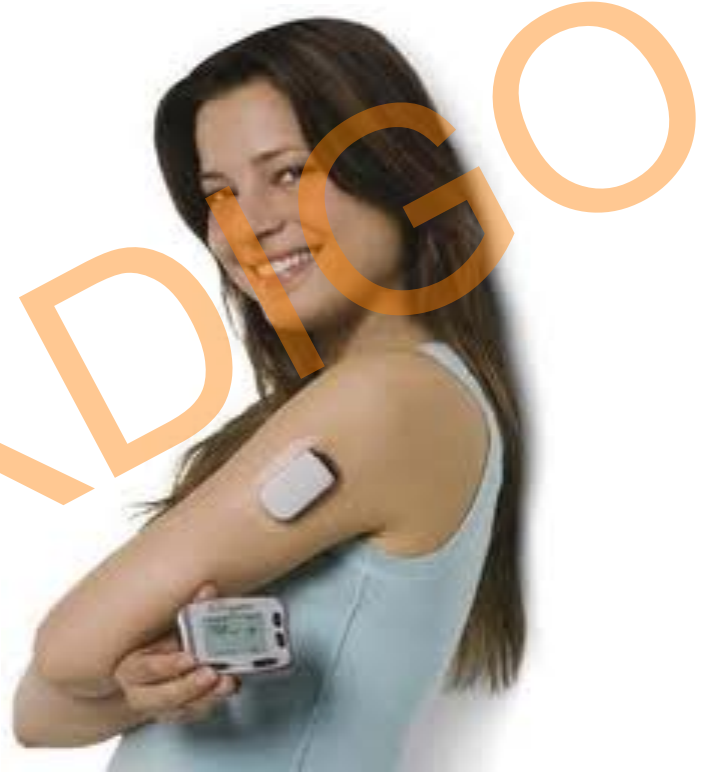


P for interaction=0.93

Strict glycemic control: side effects? *Hypoglycemias*

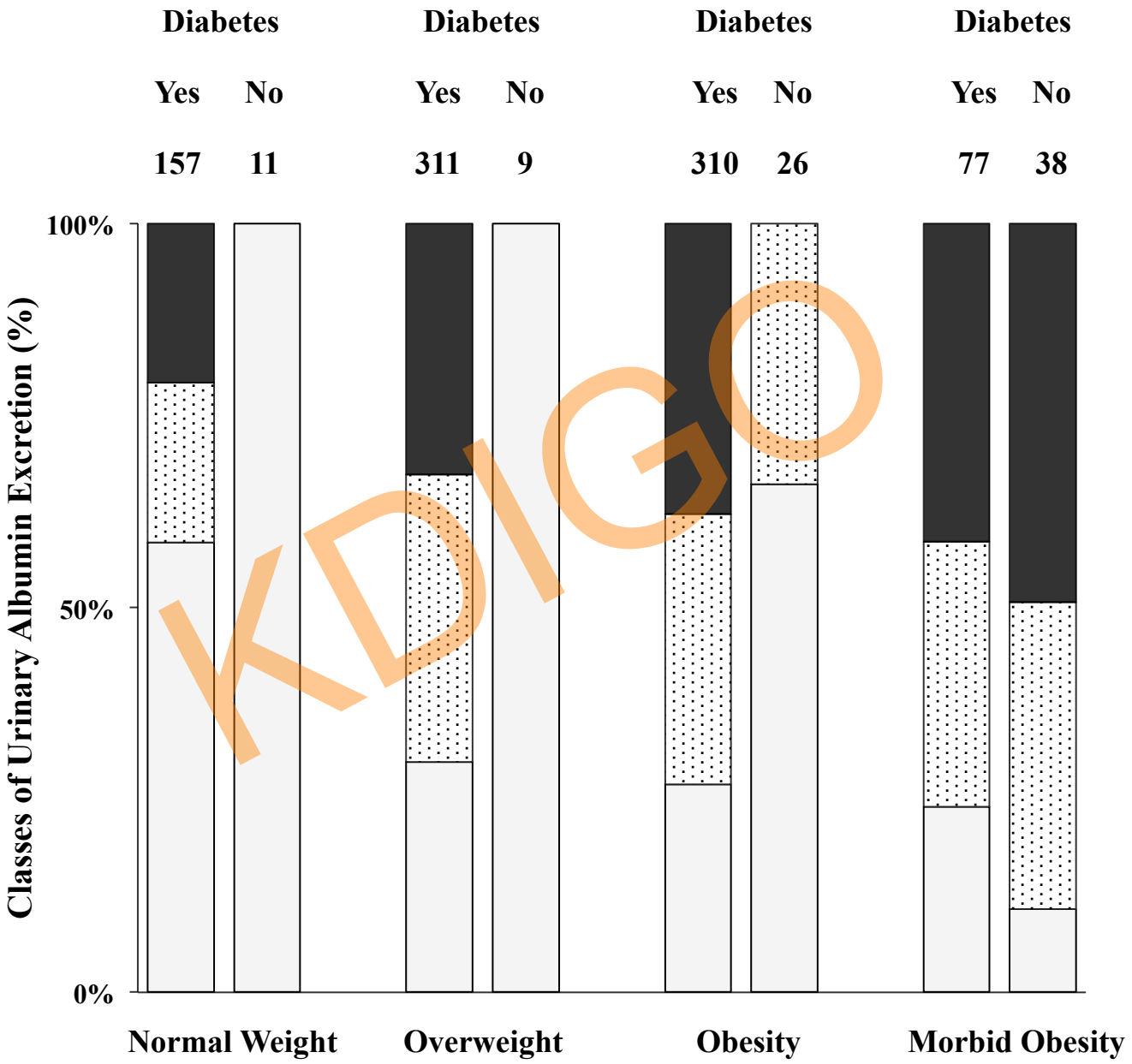
- Associations between severe hypos and adverse outcomes?
- ACCORD, ADVANCE: no association regarding temporality and no specificity for outcomes
- Strong argument against fear for hypos (in term of clinical outcomes): the DCCT/EDIC trial

The scenario today; what else tomorrow?



Strict glycemic control: side effects? *Weight gain: a true concern*

Interaction T2DM / Obesity status on UAE



Belhatem et al. Diabetes Research & Clinical Practice (in press)

Look Ahead: 4kg Weight Loss and 31% RRR for very high risk kidney disease

(Lancet Diab Endoc, 2014)

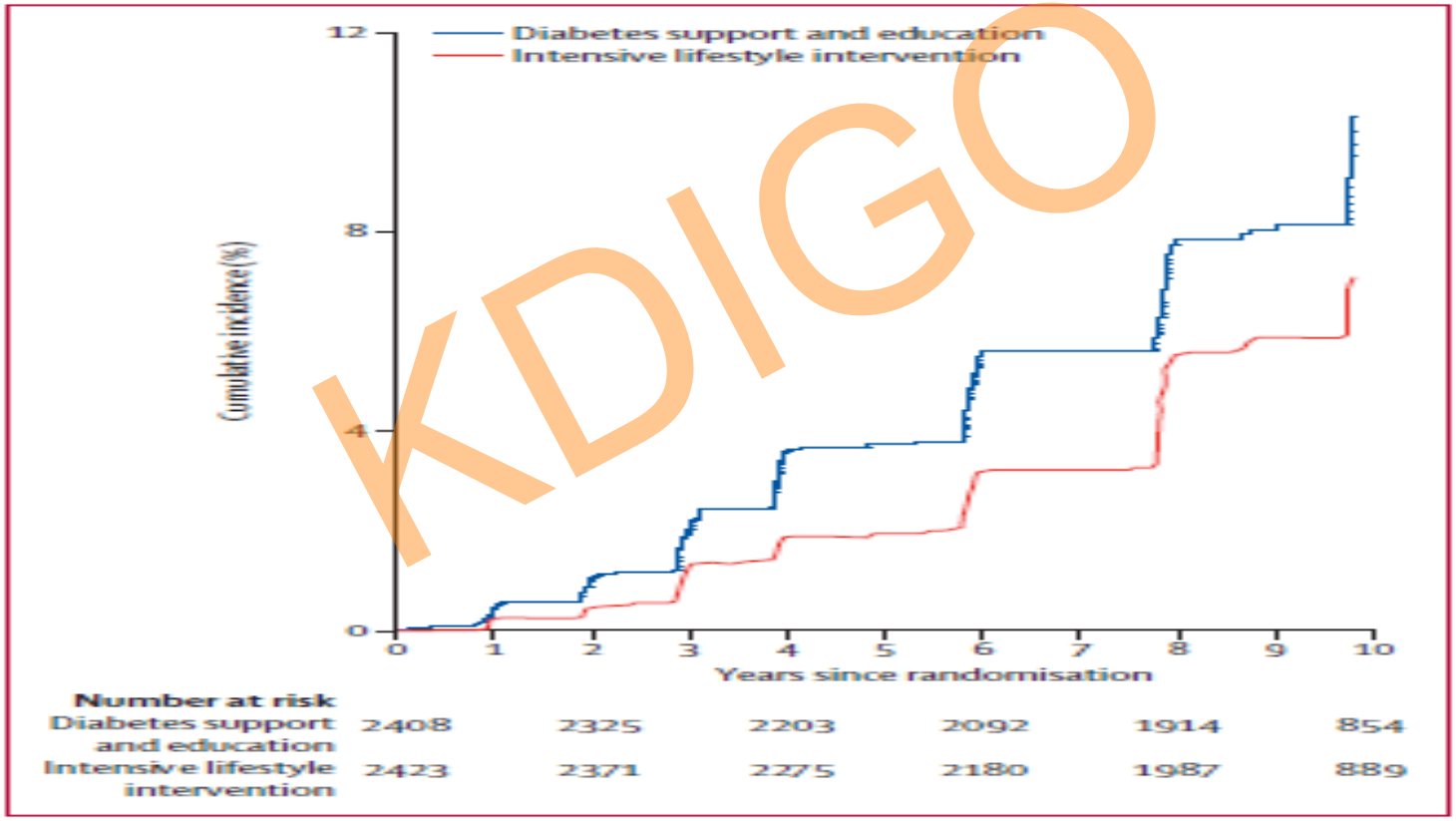


Figure 2: **Cumulative incidence of very-high-risk chronic kidney disease**
Too few observations were available beyond year 10 for reliable estimates.

Strict glycemic control: which drugs?

- Safety concerns: CV rather than µvasc outcomes
- Strict glycemic control beneficial for kidney function: specific to a given drug class???
- Mandatory knowledge of drug pharmacodynamics/pharmacokinetics

Thank you for your attention!