Impact of Recent Clinical Trials on The Management of Cardiovascular Disease in Diabetes

Glycemic Control-ADVANCE, VADT, ACCORD etc.

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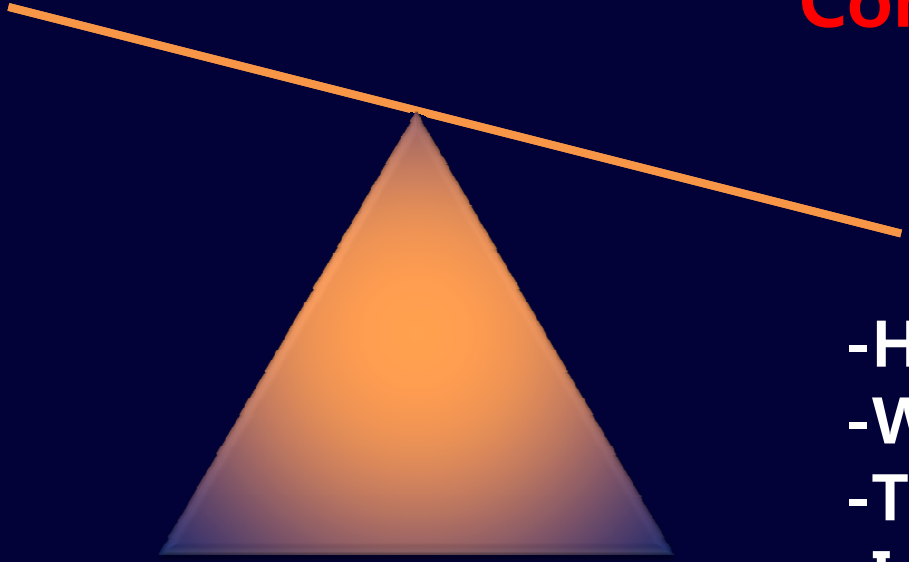
Tight Glucose Control; The Big Question

↓ CVA/Microvasc.



Age, DM duration, Vascular status, Comorbities

Negative Effects

- -Hypoglycemia
- -Wt gain
- -Time and Cost
- -Increased Mortailty

Intensive Diabetes Therapy : Reduced Incidence of Complication

HbA1C	DCCT 9 → 7.2%	Kumamoto 9→7%	UKPDS 8→7%
Retinopathy	63%	69%	17% to 21%
Nephropathy	54%	70%	24% to 33%
Neuropathy	60%	Improved	-
Cardiovascular disease	**NS**	-	16%

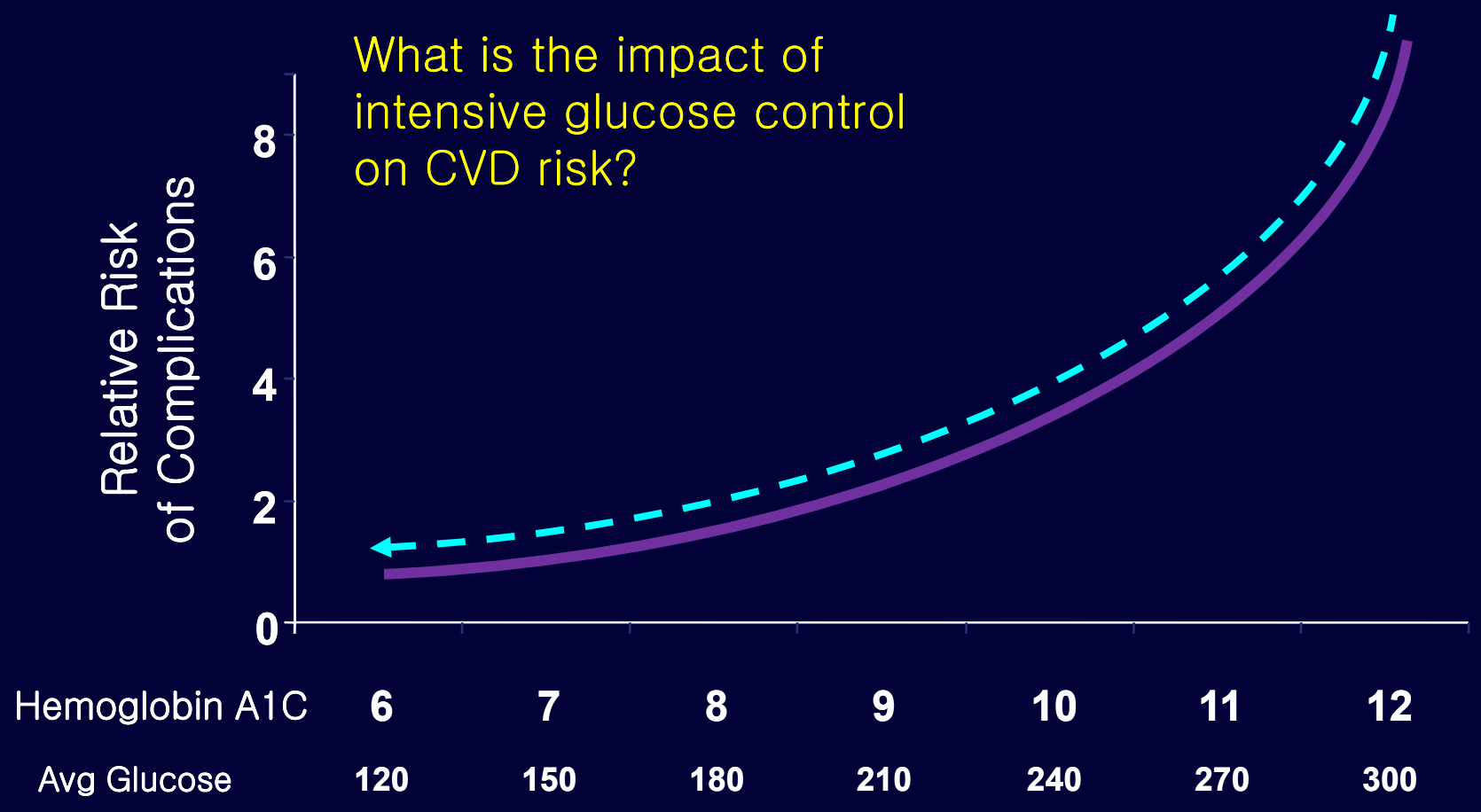
Diabetes Control and Complication Trial (DCCT) Research *Group.N Eng J med*.1993:329:977-986

Ohkubo Y et al. Diabetes Res Clin Proct.1995:28:130-117

UK Prospective Diabetes Study (UKPDS) Group.Lancet 1993:352-837-853.

Slide modified from D.Kandail-International Diabetes Center,Minneapolis

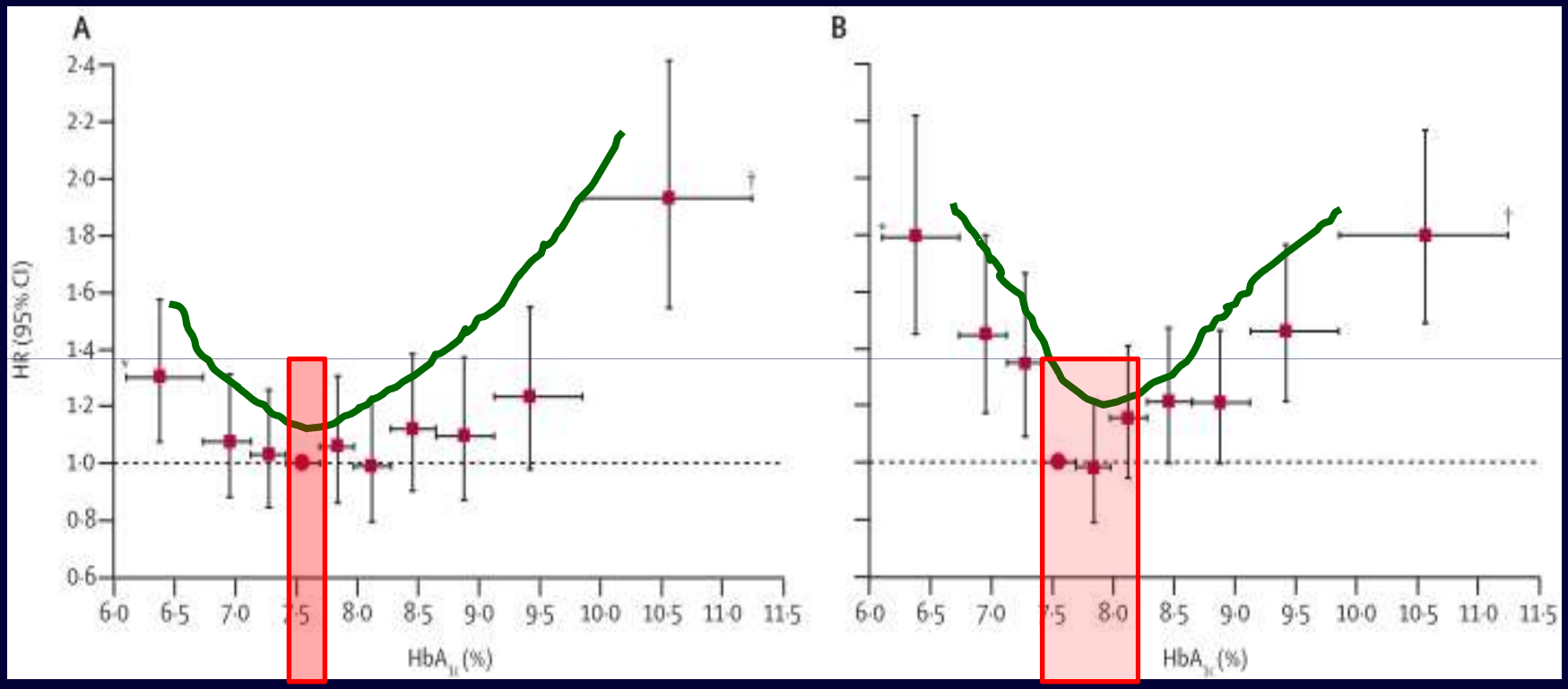
Complications Risk in Diabetes: The Impact of Intensive Glycemic Control



Adapted from: Skyler JS. *Endocrinol Metab Clin North Am* 1996 25(2):243–54. DCCT Study Group. *N Engl J Med* 1993;329:977–86. UKPDS 35 Stratton IM *et al. BMJ* 2000;321:405–12.

Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study

Adjusted hazard ratios for all-cause mortality by HbA1c



Metformin plus SU

Insulin based regimen

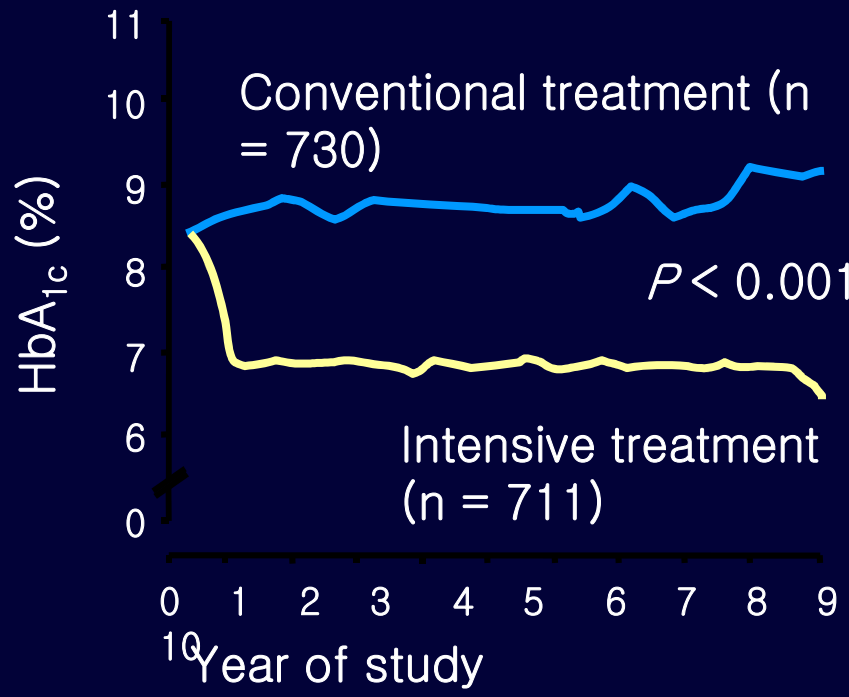
Lancet 2010; 375: 481–89

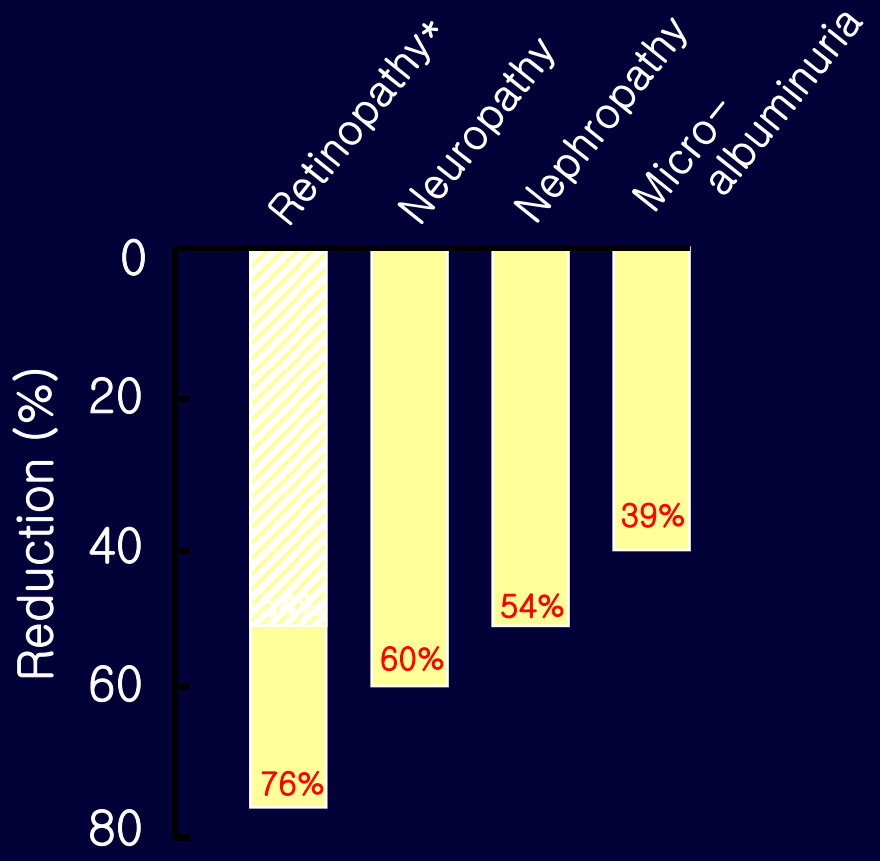
Recent Clinical Trials on The Management of Cardiovascular Disease in Diabetes

- ACCORD
- ADVANCE
- VADT
- DCCT/EDIC
- UKPDS
- Steno2

DCCT: intensive control reduces complications in type 1 diabetes

Conventional versus intensive insulin therapy (n = 1,441)

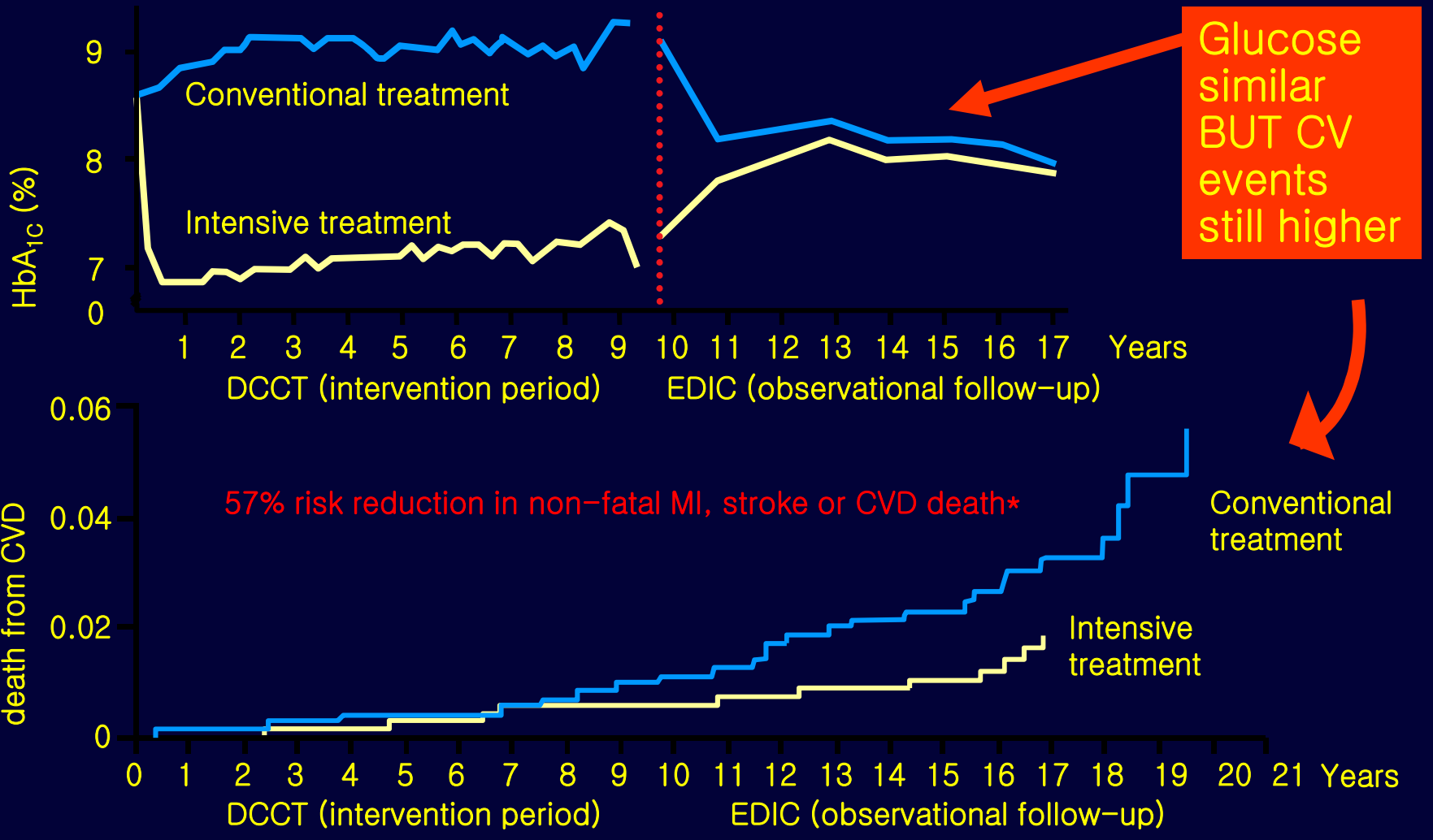




*Subdivided to primary and secondary prevention of retinopathy. Age 27 years, HbA_{1c} 8.8%. Insulin dose (U/kg/d) 0.62 (primary), 0.71 (secondary).

DCCT Research Group. *N Engl J Med* 1993; **329**:977–986.

DCCT/EDIC: long-term follow-up : metabolic memory



*Intensive vs conventional treatment.

DCCT Research Group. *N Engl J Med* 1993; **329**:977–986.
Nathan DM, *et al. N Engl J Med* 2005; **353**:2643–2653.

Legacy Effect of Earlier Glucose Control

"결론적으로 UKPDS에서는 연구 종료 후 연장된 추적 관찰에서 심근경색의 위험과 모든 원인으로 인한 사망을 줄이는 것으로 나타남"

시험완료 **8.5**년(중앙값) 후 추적 관찰시

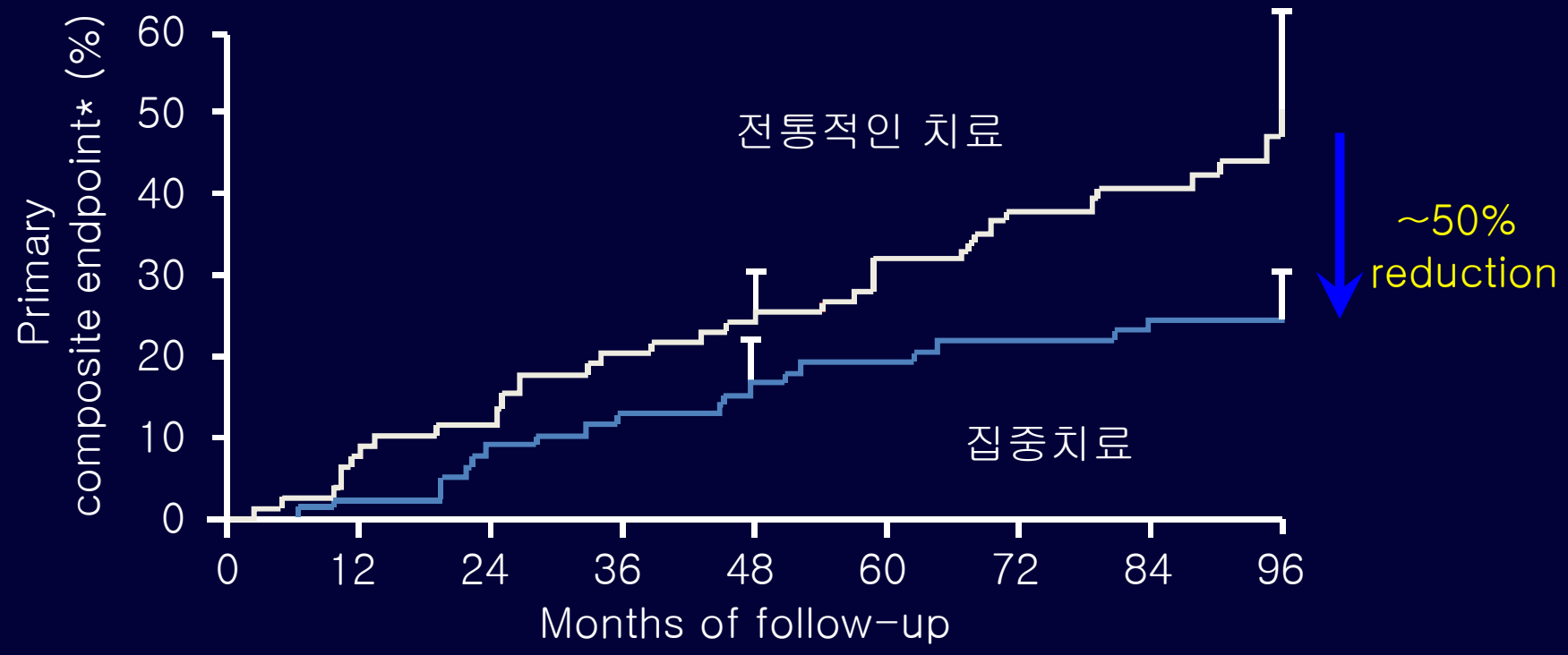
모든 종말점		**1997**	**2007**
모든 당뇨병 관련 종말점	RRR:	12%	**9%**
	p:	0.029	**0.040**
미세혈관질환	RRR:	25%	**24%**
	p:	0.0099	**0.001**
심근경색	RRR:	16%	**15%**
	p:	0.052	**0.014**
모든 원인 사망율	RRR:	6%	**13%**
	p:	0.44	**0.007**

RRR = 상대적 위험도 감소 (relative risk reduction), p = log rank

Glycemic Control and CVD : In young or early stage of diabetes

- DCCT: Possible long term CVD benefit in "young" type 1 DM, with large A1C separation to 7-CVD benefit is slow
- UKPDS-possible benefit in new onset DM with long term follow up.
- Evidence for metabolic memory-perhaps indicating benefits of good glycemic control in earlier stages of diabetes/Vascular health
- Raises possibility also of "negative glycemic memory"

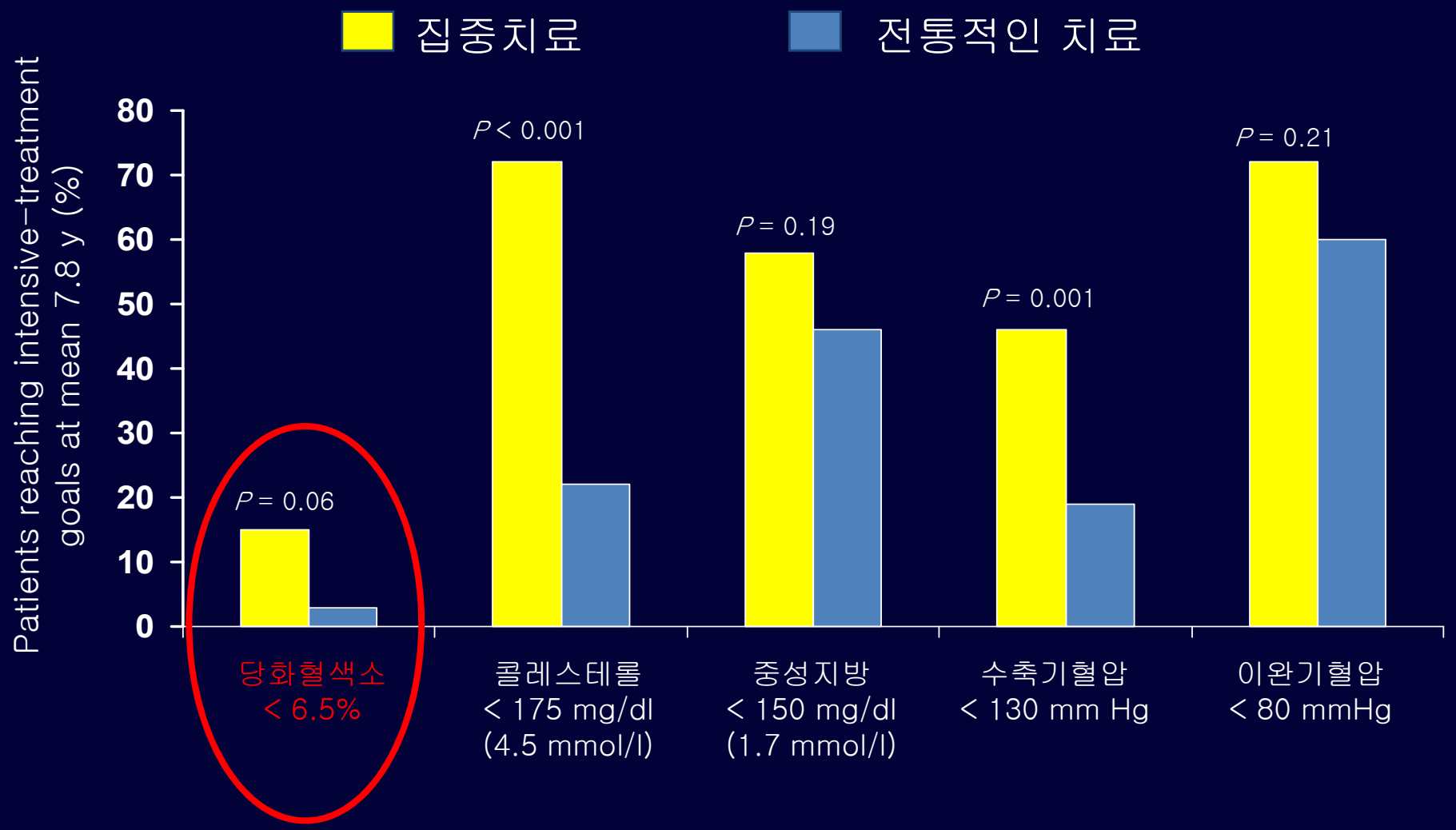
Steno-2연구:혈당, 혈압, 지질 심혈관질환에 대한 치료효과



심혈관질환과 미세혈관 합병증을 50%나 감소

Gaede P, *et al. N Engl J Med* 2003; 348:383–393.

Steno-2연구: 목표 도달률



Adapted from Gaede P, *et al*. *N Engl J Med* 2003; 348:383–393.

Recent Clinical Trials on The Management of Cardiovascular Disease in Diabetes

- ACCORD
- ADVANCE
- VADT
- DCCT/EDIC
- UKPDS
- Steno2

Comparison of Recent Glycemia Trials ACCORD, ADVANCE and VADT

Characteristic	ACCORD	ADVANCE	VADT
N	10,251	11,140	1,791
Mean Age	62	66	60.4
Duration of T2DM	10 yr	8 yr	11.5 yr
History of CVD	35%	32%	40%
BMI	32	28	31
Baseline A1C	8.3%	7.5%	9.4%

ACCORD Study Group. *N Engl J Med* 2008;358:2545–59.
ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–72.
Duckworth W *et al*. *N Engl J Med* 2009;360:129–39.

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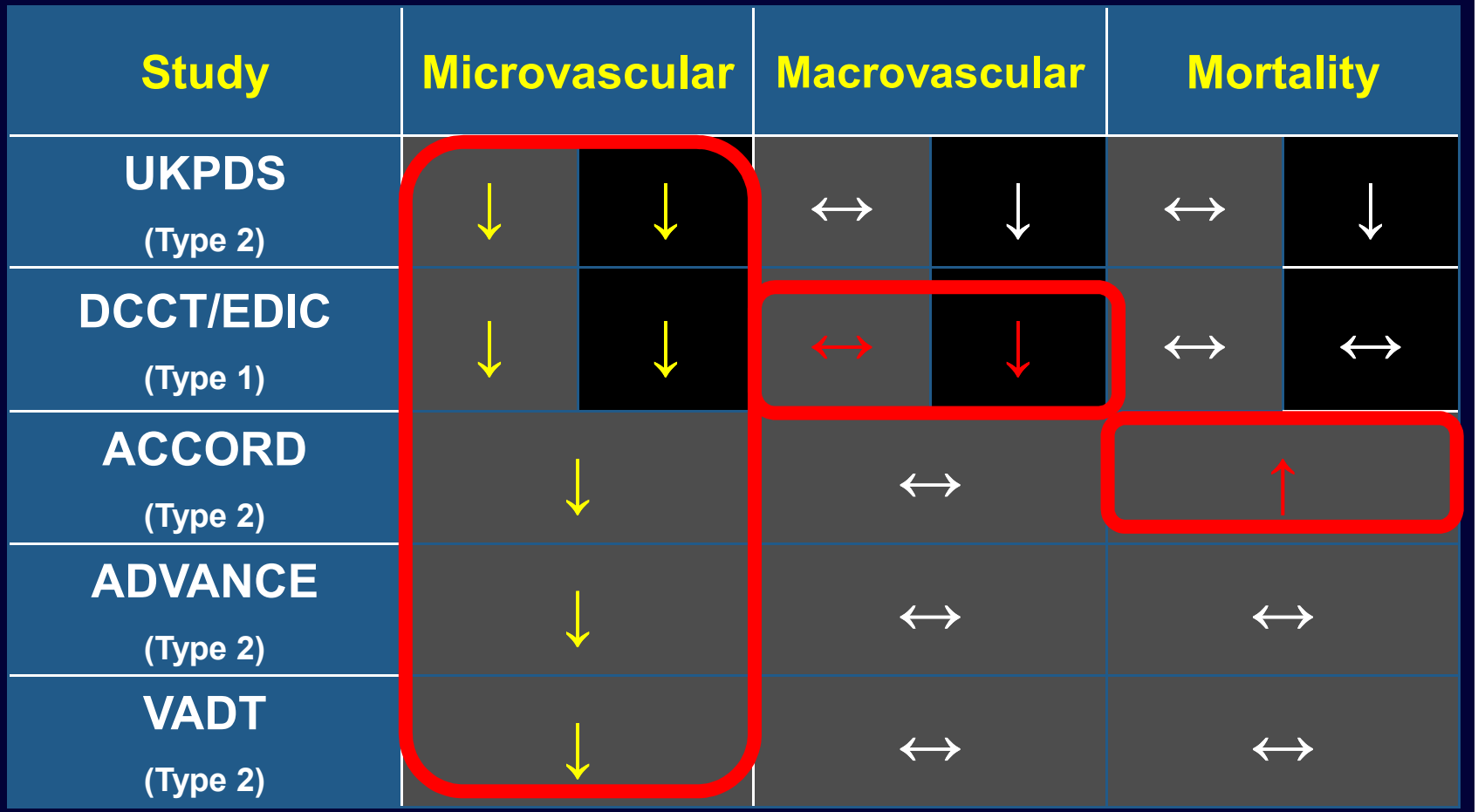
BMI	32	28	31
Baseline A1C	8.3%	7.5%	9.4%
A1C Achieved	**6.4% vs. 7.5%**	**6.5% vs. 7.3%**	**6.9% vs. 8.4%**
RRR CVD Events	**0.90** (0.78 – 1.04)	**0.94** (0.84 – 1.06)	**0.88** (0.74 – 1.05)
RRR Mortality	**1.22** (1.01 – 1.46)*	**0.93** (0.83 – 1.06)	**1.07** (0.80 – 1.42)

ACCORD Study Group. *N Engl J Med* 2008;358:2545–59.
ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–72.
Duckworth W *et al*. *N Engl J Med* 2009;360:129–39.

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials



UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854–65. Holman RR. *N Engl J Med* 2008;9;359(15):1577–89. DCCT Research Group. *N Engl J Med* 1993;329:977–86. Nathan DM *et al. N Engl J Med* 2005;353:2643–53. Gerstein HC *et al. N Engl J Med* 2008;358:2545–59. Patel A *et al. N Engl J Med* 2008;358:2560–72. Duckworth W *et al. N Engl J Med* 2009;360:129–39.

ACCORD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

- **Patients had established T2D and either established CVD or additional CV risk factors**
- **N = 10,251, projected median follow-up of 5.6 years(discontinue 3.5 years)**
- **Average Age : 62.2 yrs**
- **Median duration of Diabetes : 10 yrs**
- **Previous CV events : 35.6%**
- **HbA1c : 8.3%**
- **Study evaluated effects of intensive vs standard control of glycemia, lipids, and BP**
- **Primary Endpoint : MACE (non-fatal MI/stroke, CV death)**

N Engl J Med 2008;358:2545-59

ACCORD

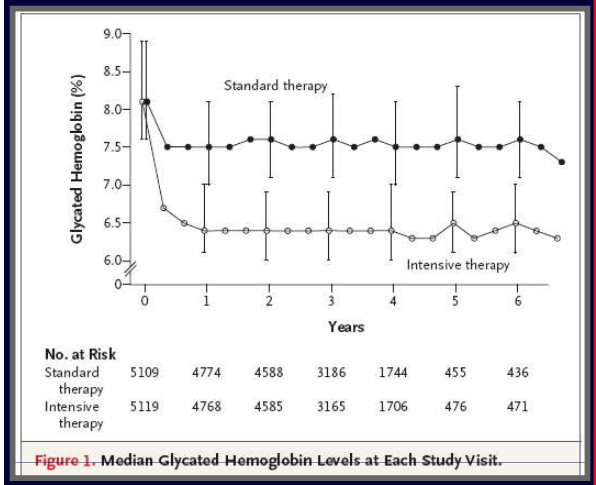
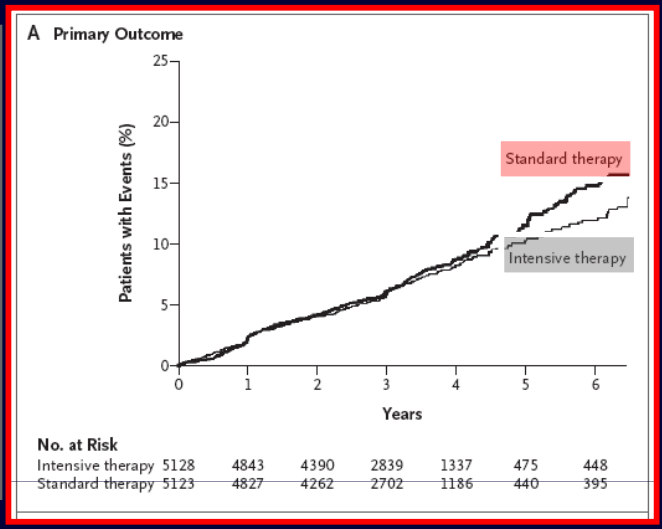
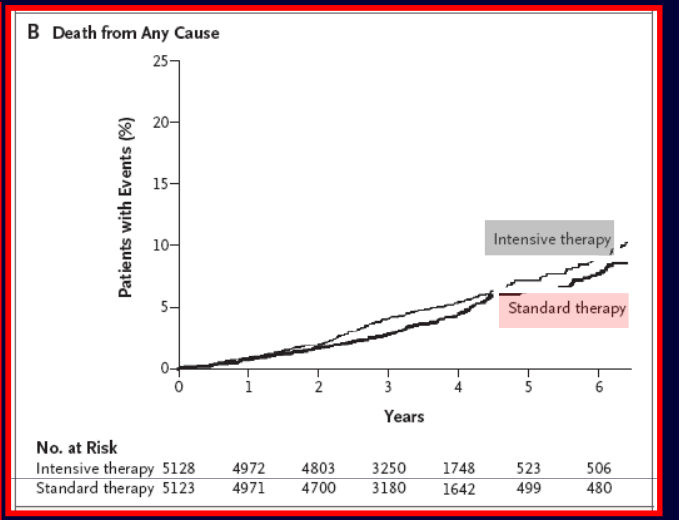


Figure 1. Median Glycated Hemoglobin Levels at Each Study Visit.





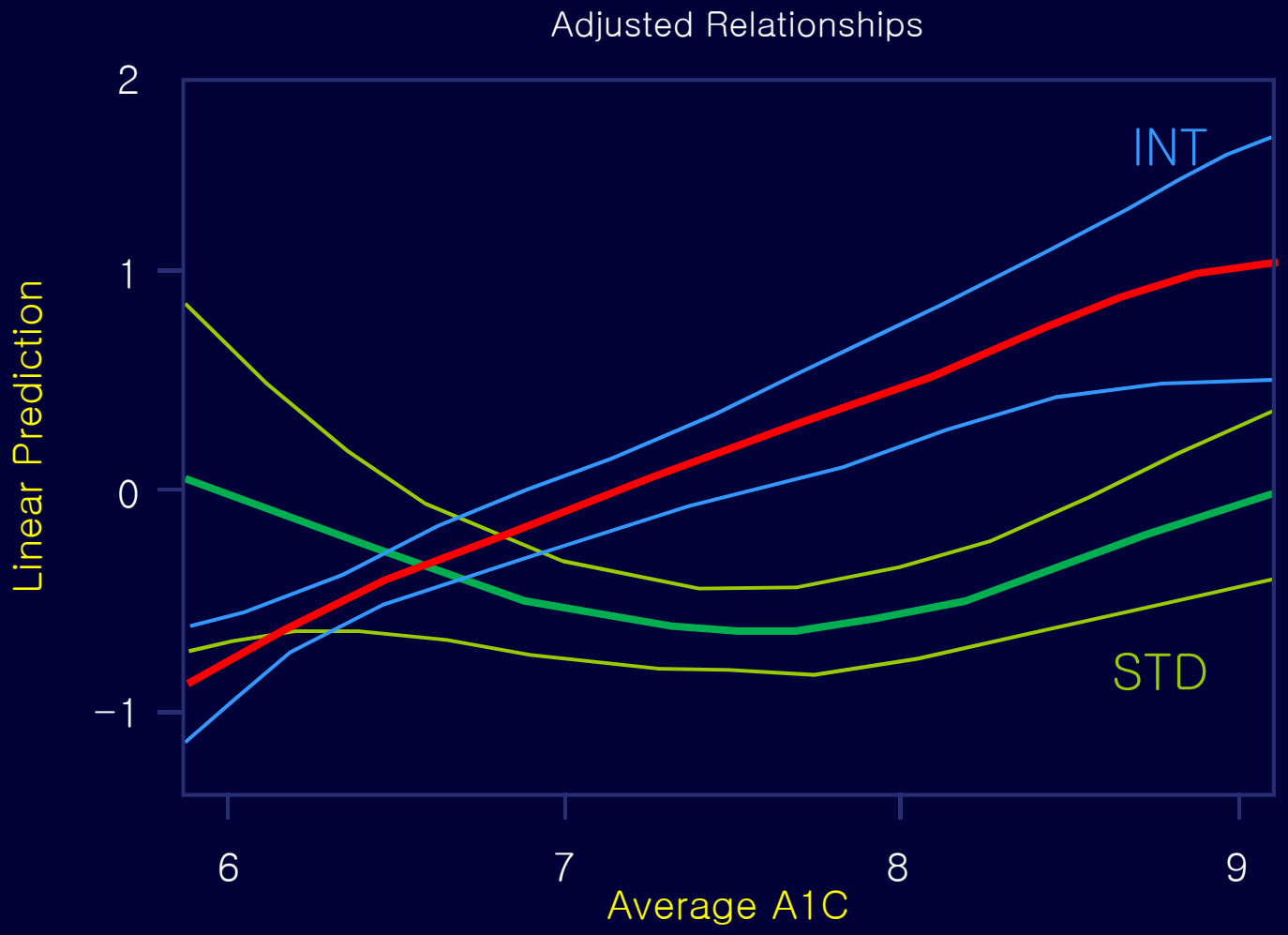
- **Higher incidence of deaths in the intensive treatment group (HbA1c <6.0%) vs the standard treatment group (HbA1c 7.0% to 7.9%)[2]**

	Intensive glycaemic control (HbA_{1c} <6.0%)	Standard glycaemic control (HbA_{1c} 7.0–7.9%)	Difference
Deaths, n	257	203	54
Rate per 1,000 patients/year	14	11	3

Average duration of treatment ~4 years. Intensive glycaemic control arm stopped 18 months early by DSMB and patients switched to standard glycaemic control

N Engl J Med 2008;358:2545-59

Epidemiologic Relationships Between A1C and All-cause Mortality in the ACCORD Trial



Riddle M *et al*. Late Breaking Clinical Trials. ADA Annual Scientific Sessions 2009. New Orleans LA. ***Diabetes Care*** 2010;33(5):983-90.

A1C and Mortality in ACCORD

- Summary
  - A 1% greater ~A1C associated with a 22% increase in annual mortality
  - Similar to the 14% increase in mortality with a 1% higher A1C in UKPDS
  - With the intensive treatment strategy there was a strong relationship between higher average A1C and greater mortality
    - 66% greater for 1% higher average A1C($p<0.0001$)
- These analyses do not implicate low A1C *per se* as a likely contributor to the increased mortality with intensive treatment in ACCORD

Riddle M *et al*. Late Breaking Clinical Trials. ADA Annual Scientific Sessions 2009. New Orleans LA. ***Diabetes Care*** 2010;33(5):983-90.

ADVANCE

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ORIGINAL ARTICLE

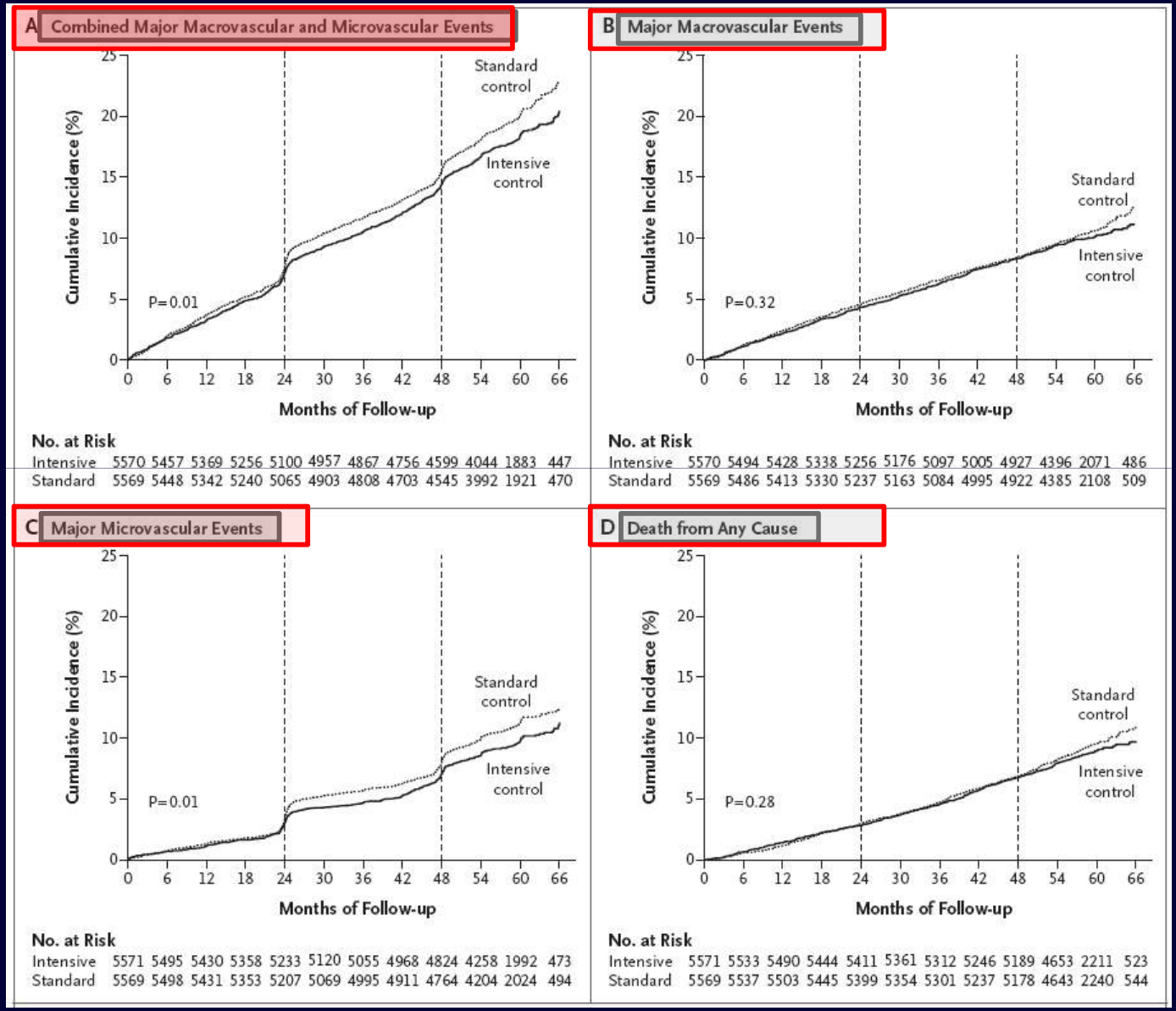
Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

- **Evaluated intensive (mean 6.5%) vs standard (mean 7.3%) glycemic control on a composite endpoint of : major macrovascular events (CV death, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy)**
- **N = 11,140, projected median follow-up of 5.0 years**
- **Average Age : 66 yrs**
- **Median duration of Diabetes : 8.0 yrs**
- **History of major macrovascular disease : 32.2 %**
- **HbA1c : 7.51%**

N Engl J Med 2008;358:2560-72

ADVANCE



N Engl J Med 2008;358:2560-72

VADT (Veterans Affairs Diabetes Trial)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ORIGINAL ARTICLE

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

- **N = 1792, follow-up of 5 to 7 years**
- **Average Age : 60.3 yrs**
- **Median duration of Diabetes : 11.5 yrs**
- **HbA1c : 9.4%**
- **More than 40% of participants had prior CV events, 80% had hypertension, 50% had lipid abnormalities, and majority were obese**
- **Previously uncontrolled on insulin or maximum doses of one or more OADs**

강화치료군에서는 6.9%, 표준치료군에서는 8.4%

N Engl J Med 2009;360:129-39

VADT

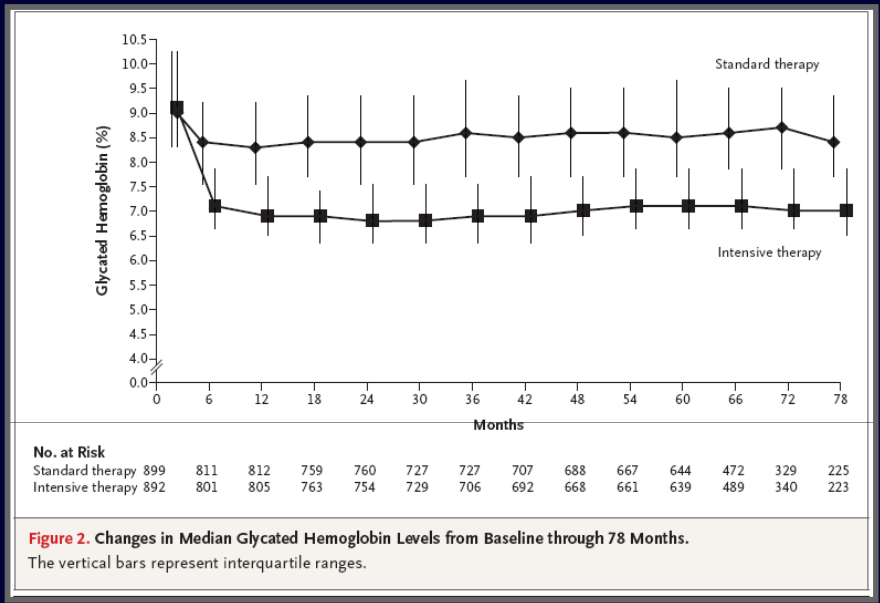
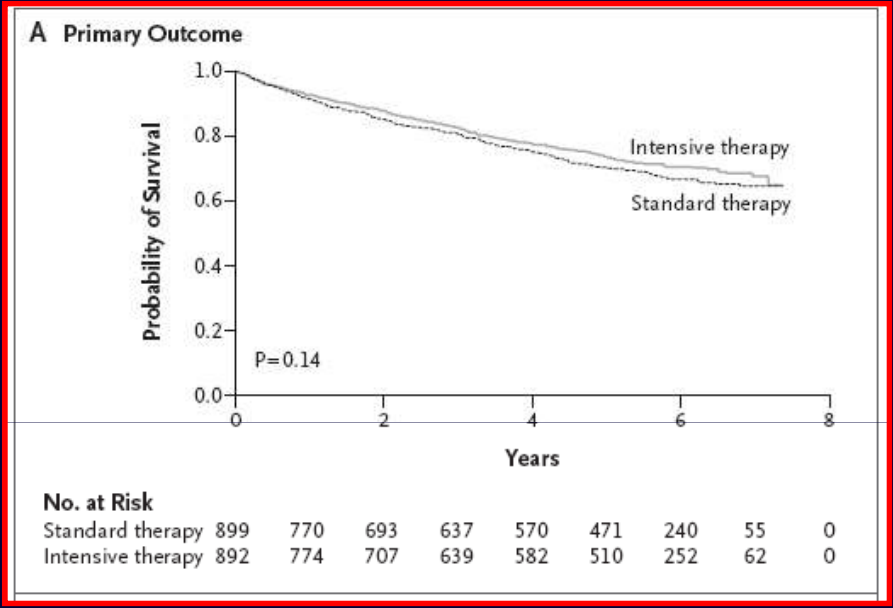


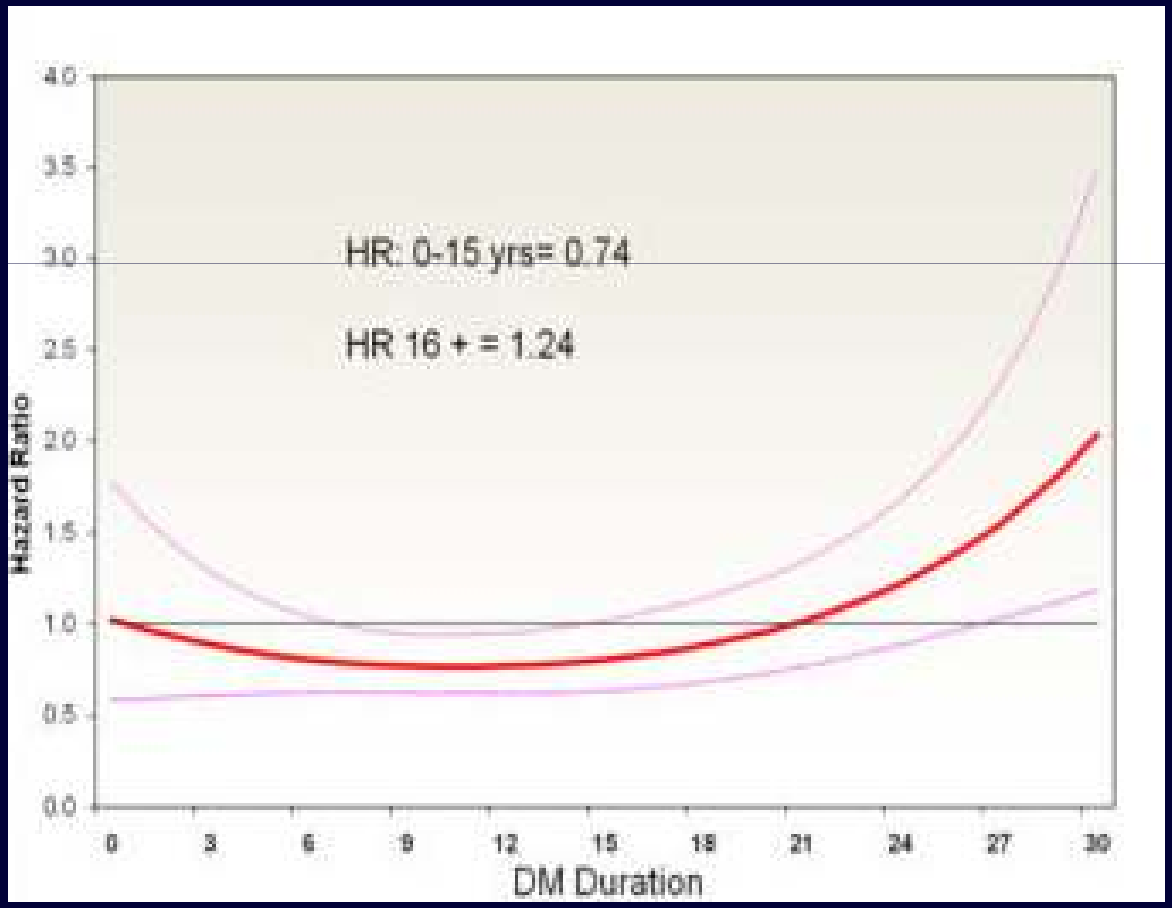
Figure 2. Changes in Median Glycated Hemoglobin Levels from Baseline through 78 Months.
The vertical bars represent interquartile ranges.



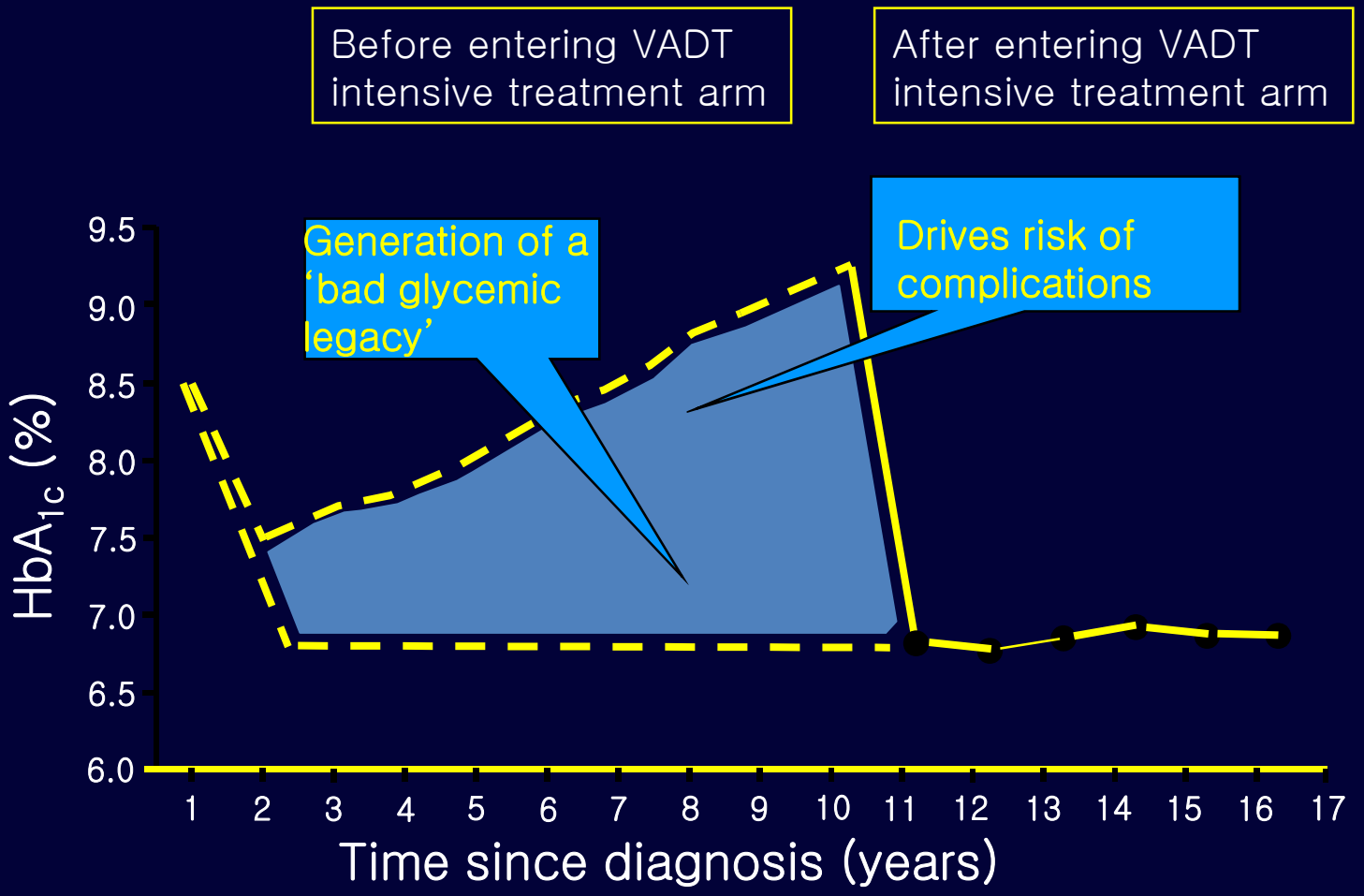
- The primary result did not show that intensive blood sugar control (HbA1c levels below 7%) had a statistically significant effect on reducing major CV events associated with diabetes

N Engl J Med 2009;360:129-39

VADT: Relationship of DM duration with CVD Outcome
(post hoc analysis)



Predictions from VADT: impact of bad glycemic legacy

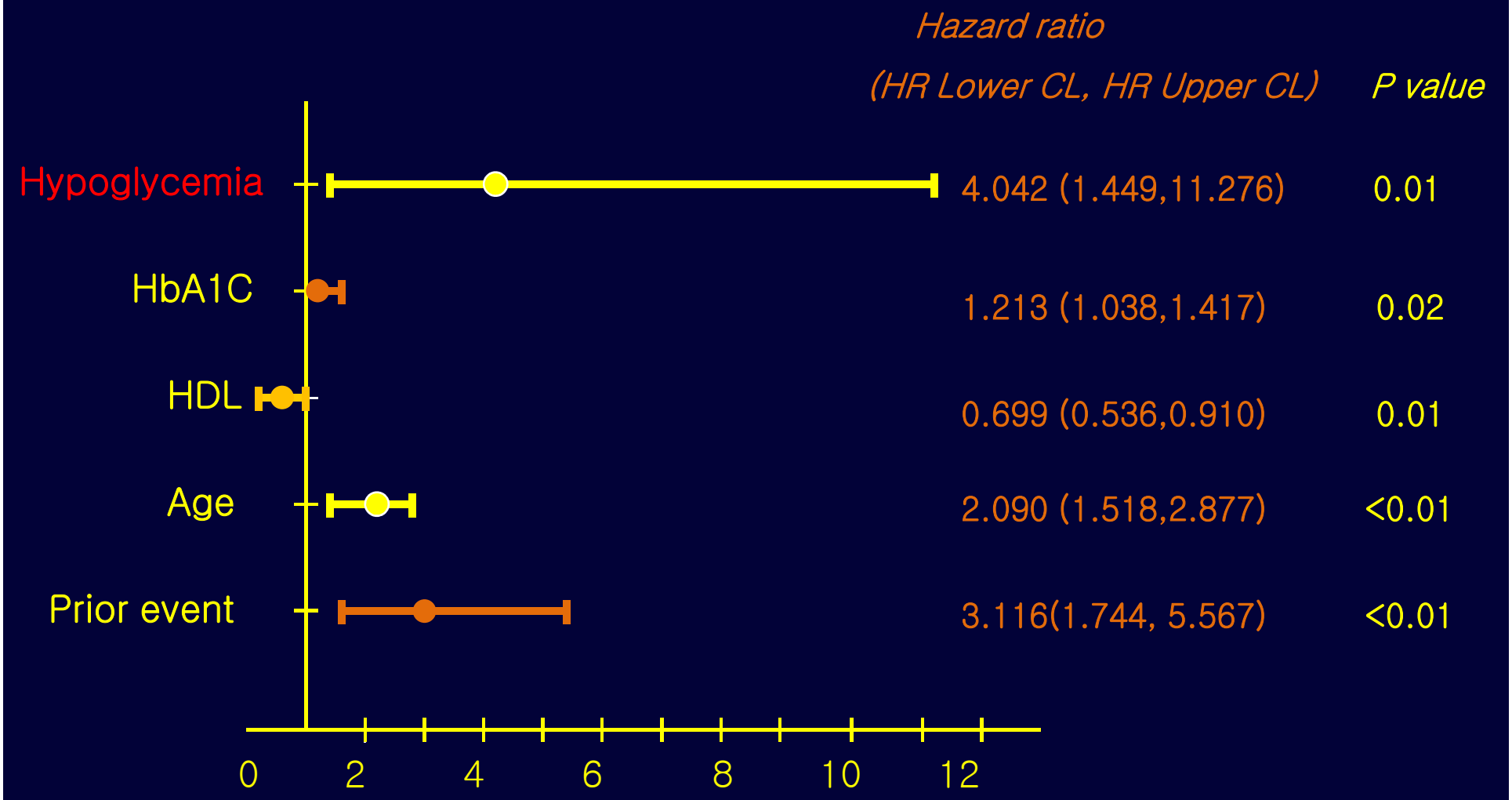


Del Prato S. *Diabetologia* 2009; **52**:1219–1226.

Hypoglycemic Episodes

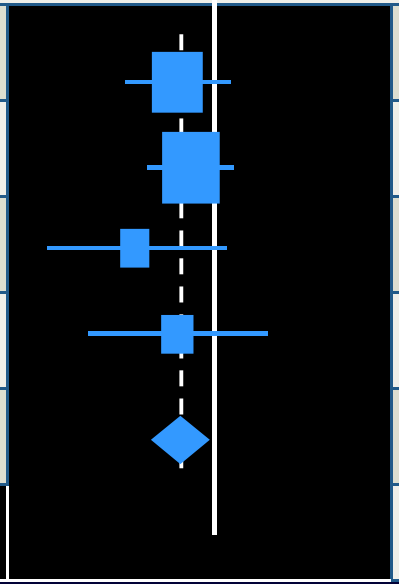
Variable	Standard Therapy(N=899)	Intensive Therapy(N=892)
	No./100 patient-yr	
Episodes with impaired consciousness	3	9
Episodes with complete loss of consciousness	1	3
Nocturnal episodes	44	152
Total episodes		
With symptoms	383	1333
Without symptoms	49	233
Relieved by food or sugar intake	421	1516
Measurement of blood glucose during episodes	348	1392
With documented blood glucose<50mg/dl (2.8mmol/liter)	52	203

Predictors of CV Death



A Broader View of CVD and Diabetes:
Implications of ACCORD, ADVANCE, UKPDS and VADT

Intensive glucose control and macrovascular outcomes in type 2 diabetes

Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA1c (%)	Favours more intensive / Favours less intensive	Hazard ratio (95% CI)
Major cardiovascular events					
ACCORD	352 (2.11)	371 (2.29)	-1.01		0.90 (0.78 - 1.04)
ADVANCE	557 (2.15)	590 (2.28)	-0.72		0.94 (0.84 - 1.06)
UKPDS	169 (1.30)	87 (1.60)	-0.66		0.80 (0.62 - 1.04)
VADT	116 (2.68)	128 (2.98)	-1.16		0.90 (0.70 - 1.16)
Overall	1,194	1,194	-0.88		0.91 (0.84 - 0.99)
					Q=1.32, p=0.72, I^2=0.0%

Turnbull FM *et al*. *Diabetologia,* published on line August 2009.

Summary of Glucose Lowing Effects on CVD by Baseline DM Stage or Vascular Age

	Early Dz	Mid-stage Dz	Late Dz
UDGP		NO*	
VA Feasibility			NO
DCCT	Yes, delayed		
UKPDS	Yes, delayed		
Advance			NO
ACCORD	possibly		NO*
VADT	possibly		NO
DIGAMI-1	possibly		?
Euro Heart S			NO

Yes-Reduced CVA, No-No benefit or *increased; UGDP increase CVD in tolbulamide

Optimal HbA1C is an Individualized Goal

General Goal HbA1C<7%

1. Risk for/from hypoglycemic
2. Low benefit of lower HbA1C(e.g,very elderly)
3. Difficult to control
4. Increased vascular age(e.g.,prior CVD + athero,long duration of DM

None True → HbA1C<6.5-7%

One True → HbA1C<7.5%

Two + True → HbA1C<7.5-8%

Modified from Eldor and Raz, diabetic studies 2009

대한내분비학회지: 제 25 권 제 1 호 2010
10.3803/jkes.2010.25.1.22

□ 지상 강좌 □

제2형 당뇨병에서 강화혈당조절과 심혈관 질환의 예방에 관한 최근 연구결과들에 대한 공동견해

대한내분비학회, 대한당뇨병학회

Intensive Glycemic Control and the Prevention of Cardiovascular Disease in Type 2 Diabetes Mellitus: A Review and Consensus

Korean Endocrine Society, Korean Diabetes Association

1. 새로 진단받은 제2형 당뇨병 환자는 조기에 철저한 혈당조절을 하는 것을 원칙으로 한다. 단, 이미 심혈관 질환이 있거나 위험성이 높은 환자에서는 목표혈당 수치를 개별적으로 설정할 필요가 있으며 다른 심혈관 질환의 위험요소들 (흡연, 운동부족, 부적절한 식사 습관, 이상지질혈증, 고혈압 등)에 대한 적극적인 관리가 필요하다.

2. 기존에 치료받고 있는 제2형 당뇨병 환자도 철저한 혈당조절을 하는 것을 원칙으로 한다. 단, 이미 심혈관 질환이 있거나 위험성이 높은 환자에서는 목표혈당수치를 개별적으로 설정할 필요가 있으며 특히 혈당강하제를 이용하여 치료할 때 혈당의 급격한 변화가 오지 않도록 점진적으로 강하시킨다. 또한 다른 심혈관 질환의 위험요소들(흡연, 운동부족, 부적절한 식사 습관, 이상지질혈증, 고혈압 등)에 대한 적극적인 관리가 필요하다.

경청해 주셔서 감사합니다