Can we reduce CV complications by targeting normal glucose levels?

김대중

아주의대 내분비대사내과

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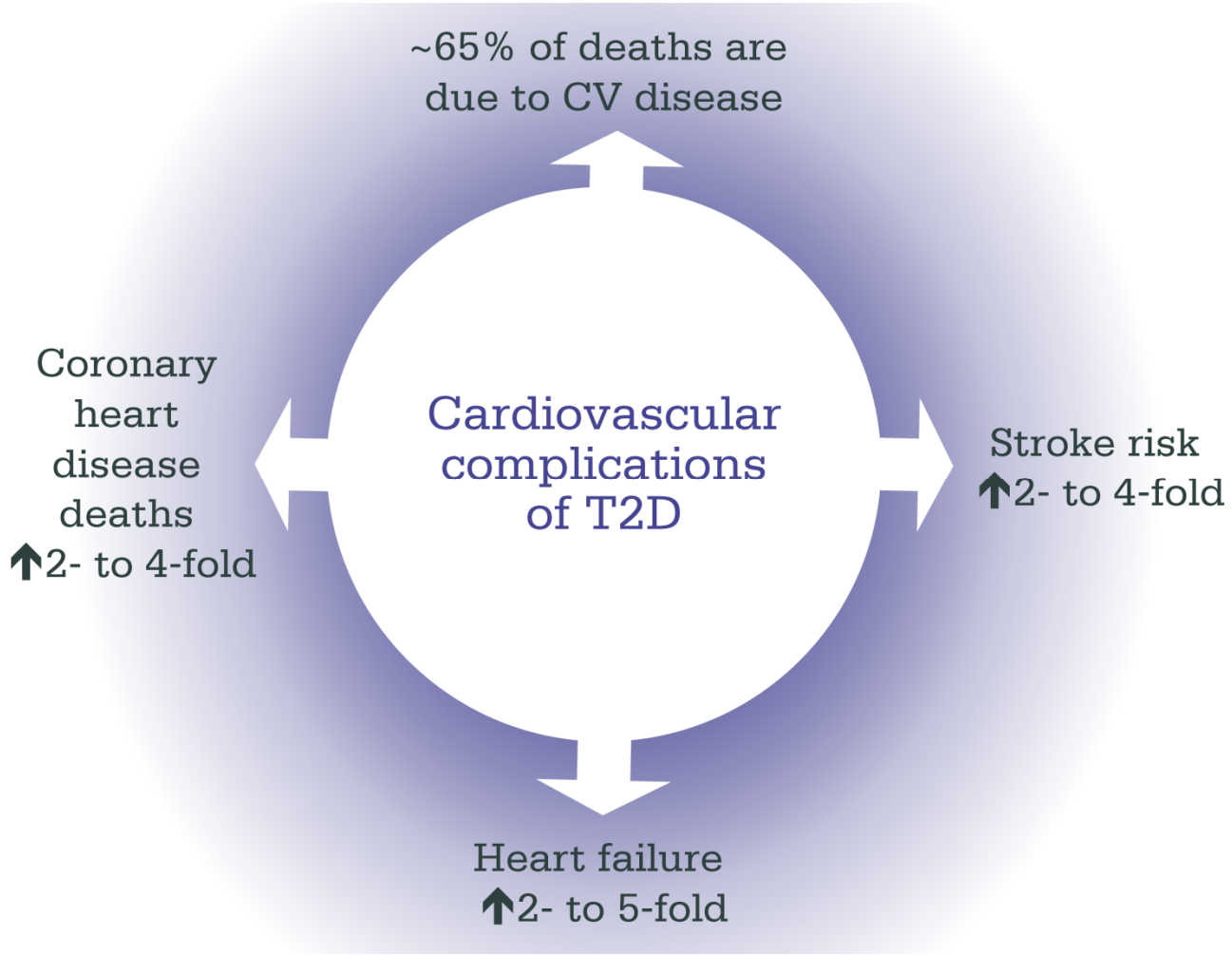
Diabetes and CV risk

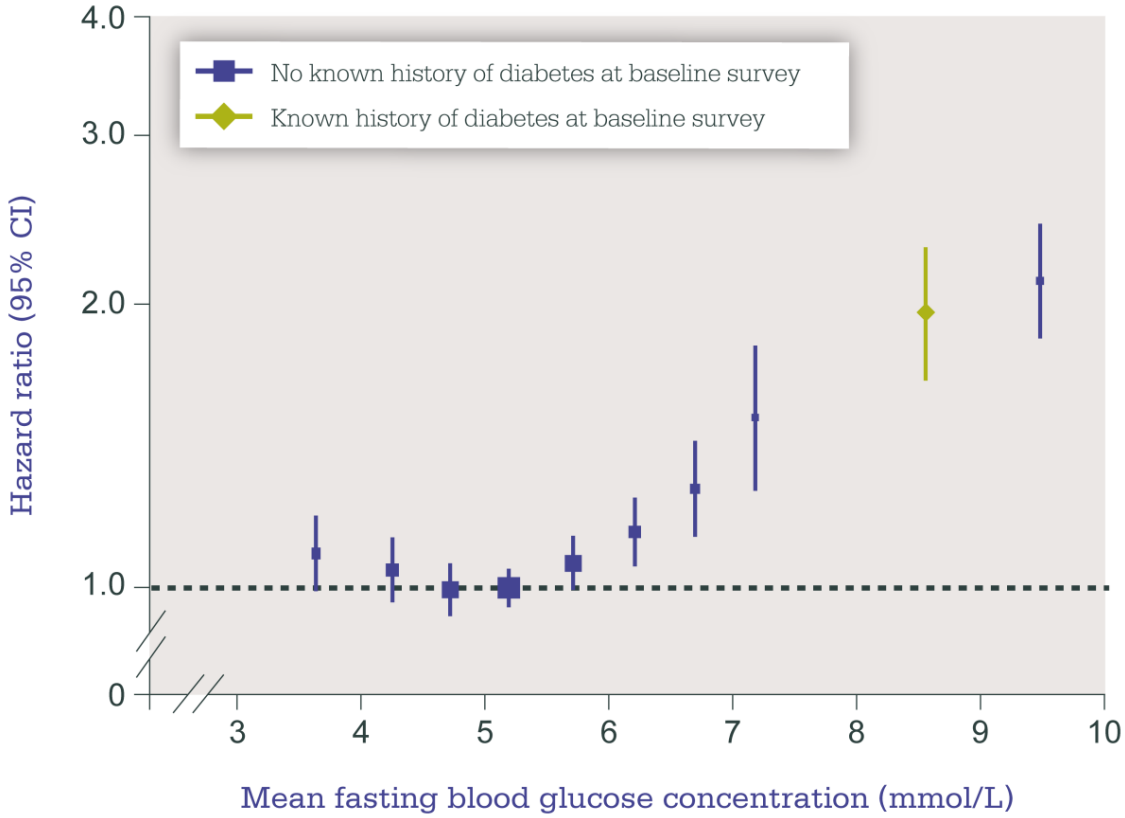
Diabetes and Cardiovascular diseases



Bell DSH. *Diabetes Care* 2003;26:2433-4.

High FPG correlates with high risk of coronary heart disease even in non-diabetic patients

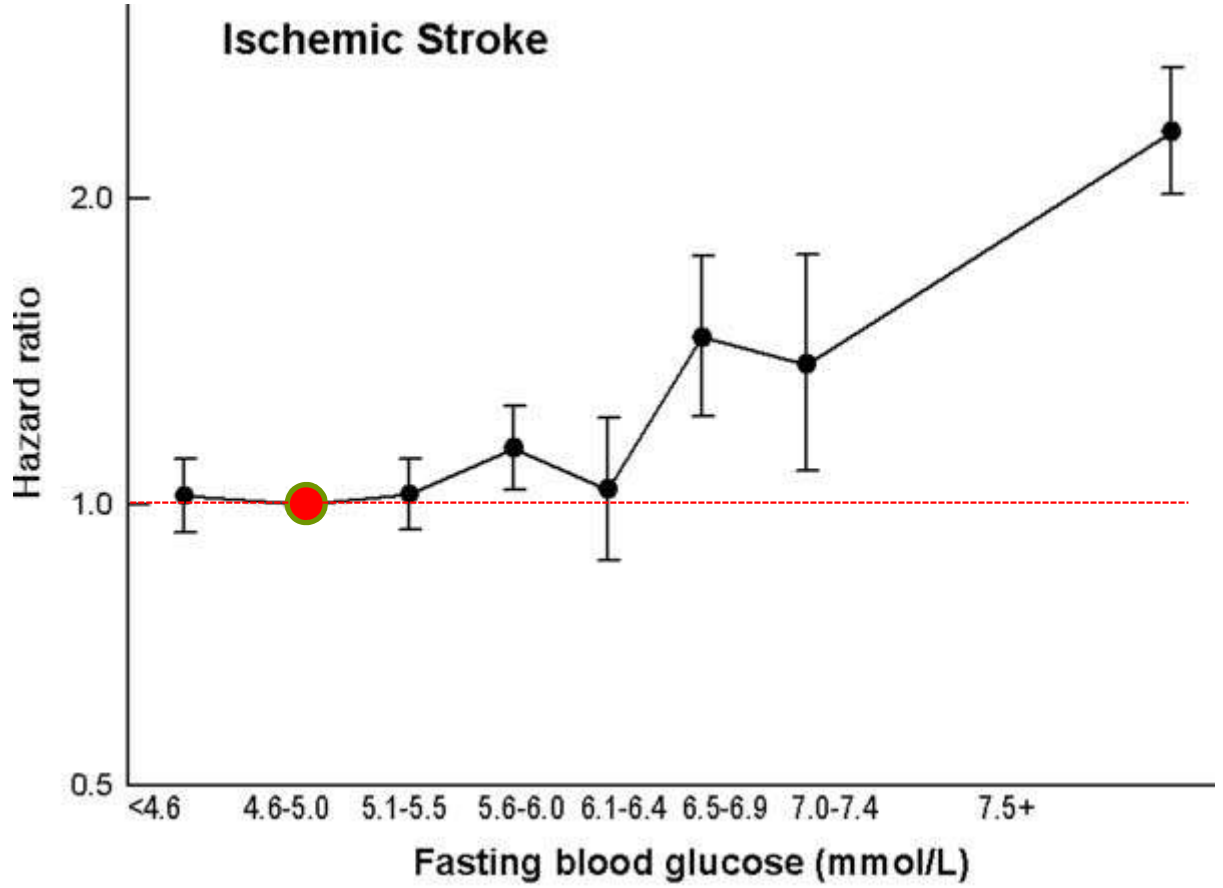
Meta-analysis of 102 prospective studies
~700,000 participants without prior cardiovascular disease



HR in figure adj. for age, smoking, BMI, SBP

The Emerging Risk Factors Collaboration. *Lancet* 2010;375:2215–22.

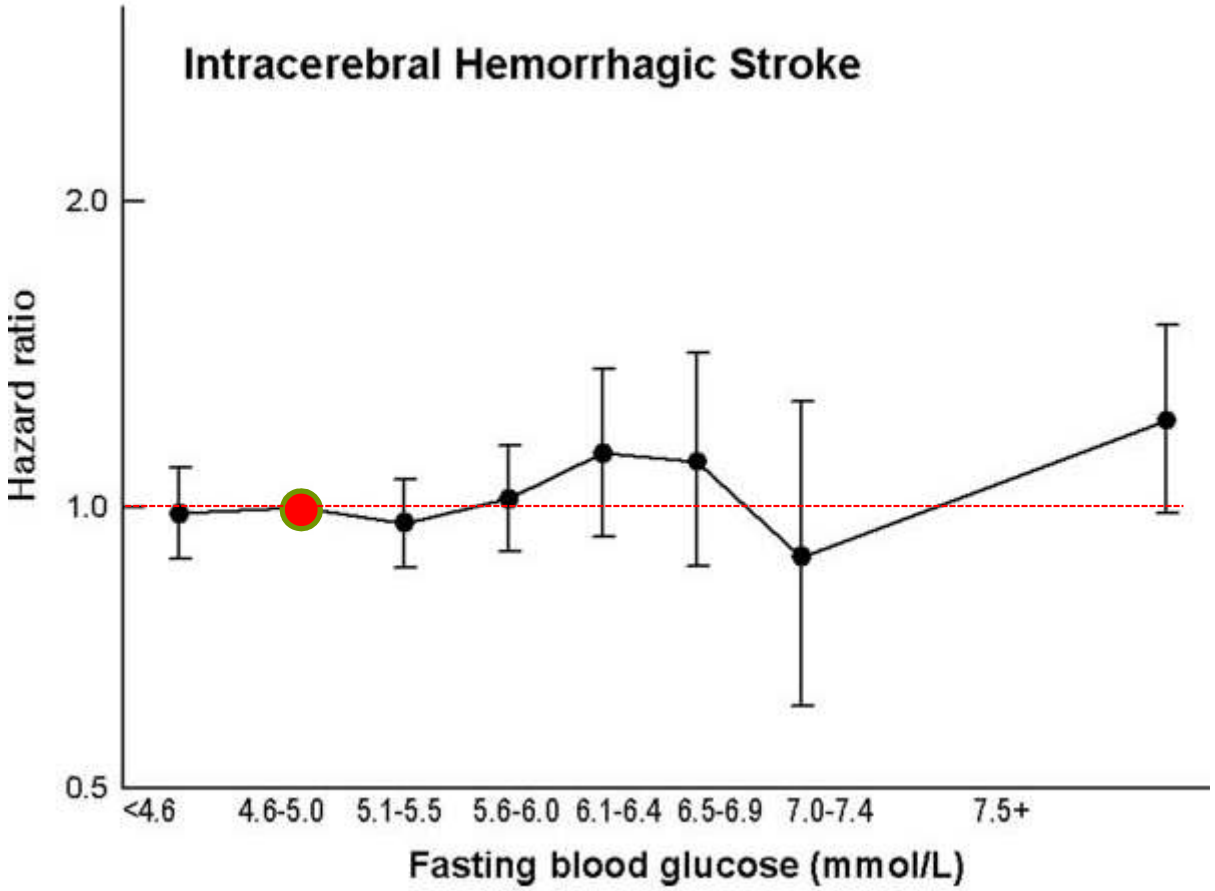
Fasting Blood Glucose and Risk of Ischemic Stroke; Korean men



*after excluding diabetes,
*adjusted for age, height, BP, TC, BMI, smoking, alcohol, regular exercise, salary, and area of residence

Circulation 2009;119;812-819

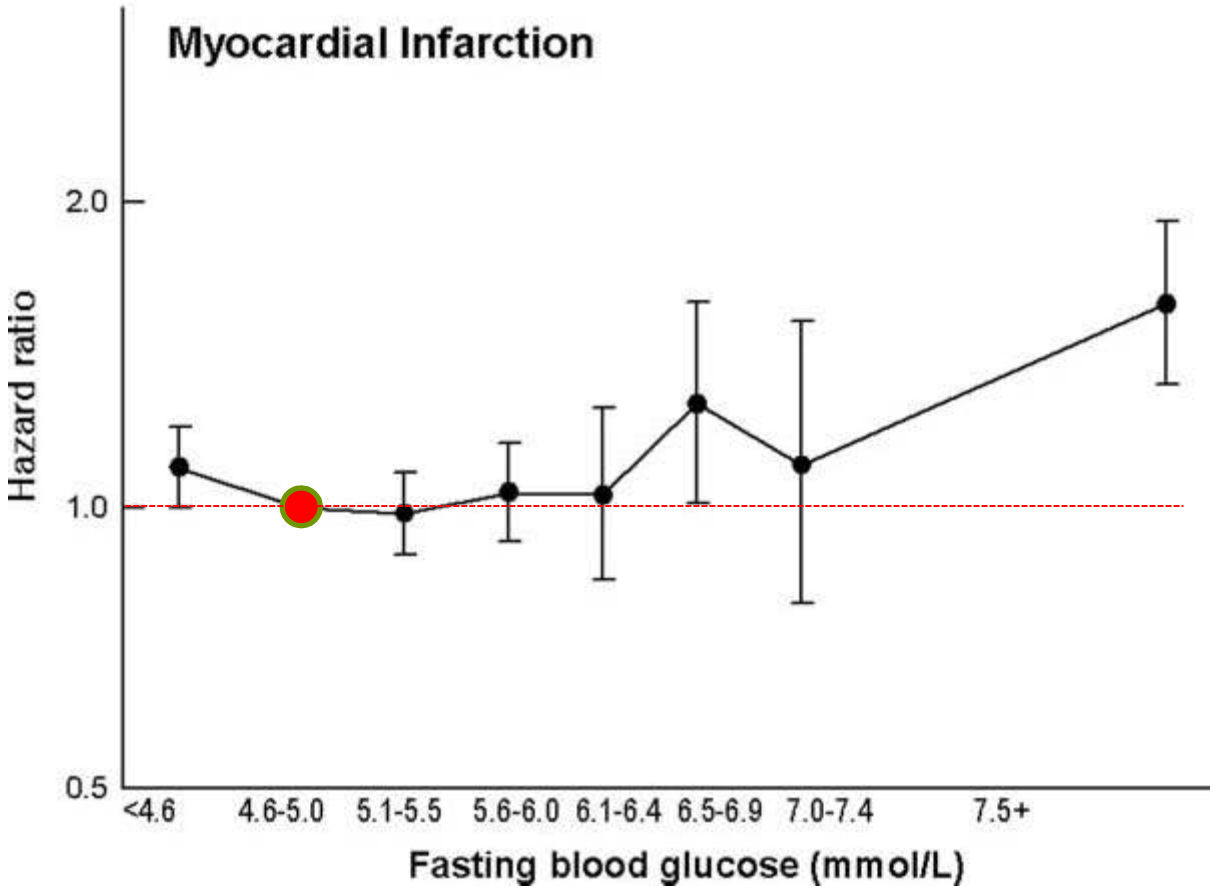
Fasting Blood Glucose and Risk of Hemorrhagic Stroke; Korean men



*after excluding diabetes,
*adjusted for age, height, BP, TC, BMI, smoking, alcohol, regular exercise, salary, and area of residence

Circulation 2009;119;812-819

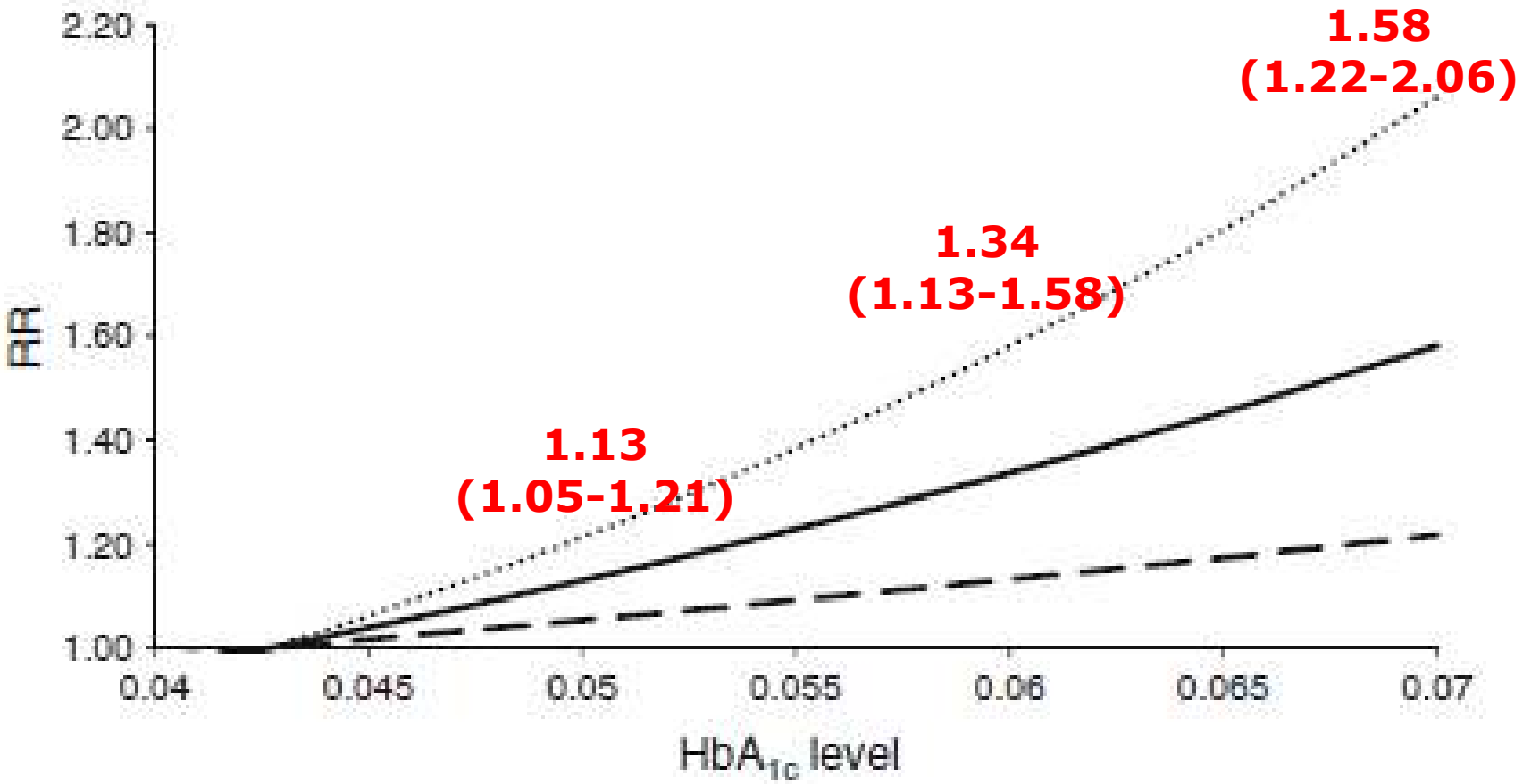
Fasting Blood Glucose and Risk of Myocardial Infarction; Korean men



*after excluding diabetes,
*adjusted for age, height, BP, TC, BMI, smoking, alcohol, regular exercise, salary, and area of residence

Circulation 2009;119;812-819

HbA1C and Cardiovascular Death in non-DM



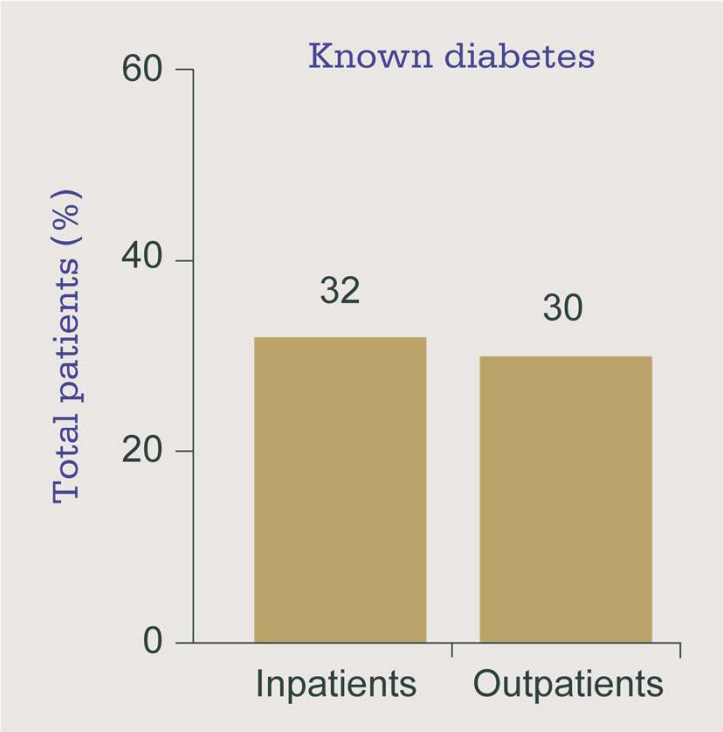
Reference : 0.0427 (4.27%)

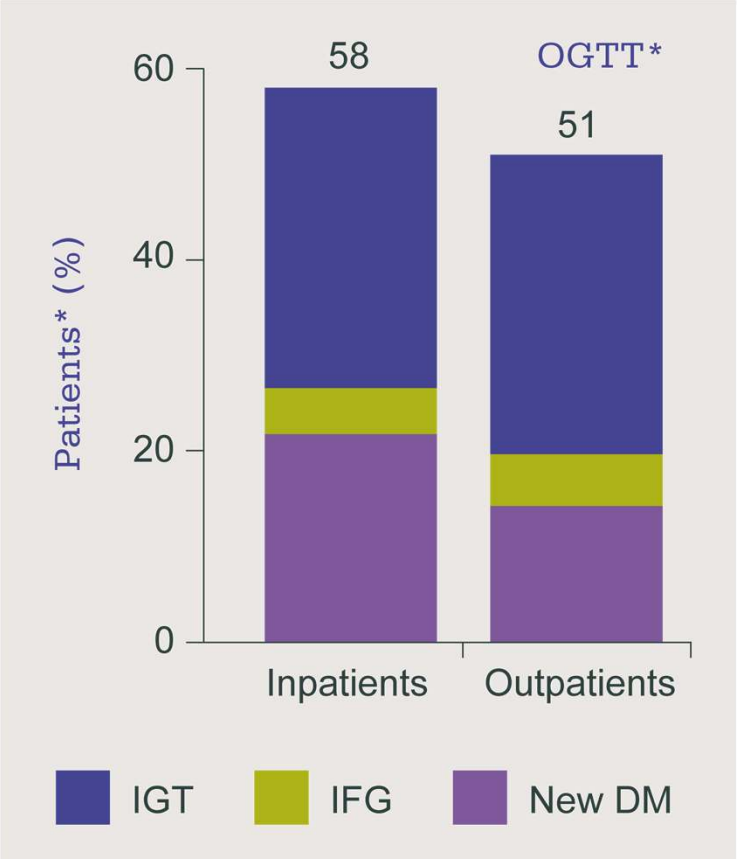
Results for **total CV events** were similar

Diabetologia. 2011 Feb

Abnormal glucose metabolism in patients with CAD

n=2107 inpatients with acute CAD; n=2854 outpatients with stable CAD

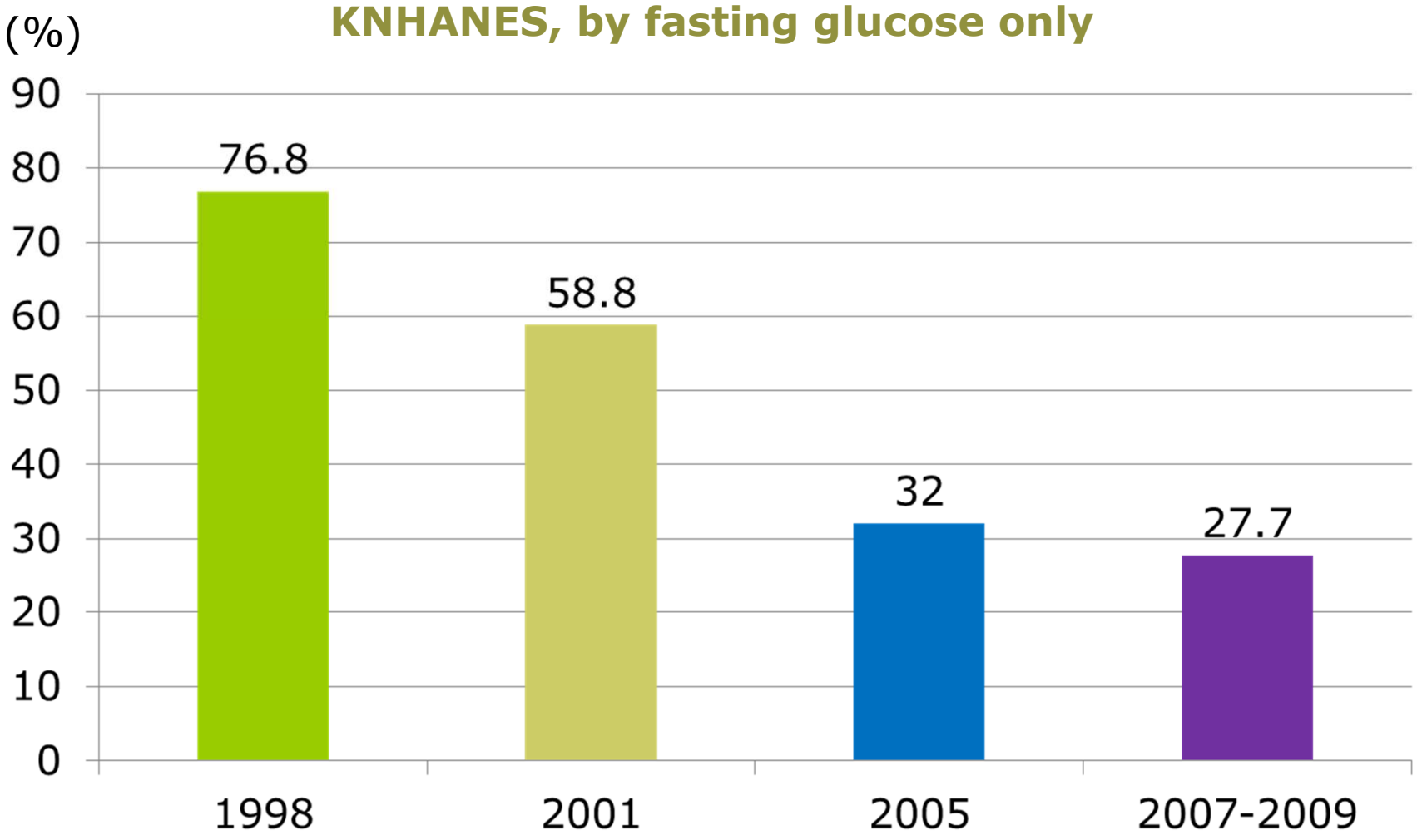




*n = 1920 without known diabetes
CAD, coronary artery disease. IGT, impaired glucose tolerance.
IFG, impaired fasting glucose. OGTT, oral glucose tolerance test.

Bartnik M, et al. *Eur Heart J* 2004;25:1880-90.

Undiagnosed diabetes in Korea



Diabetes Metab J 2011;35:303-308

Prevalence of IGT and T2D in non-diabetic men with CAD referred for coronary angiography

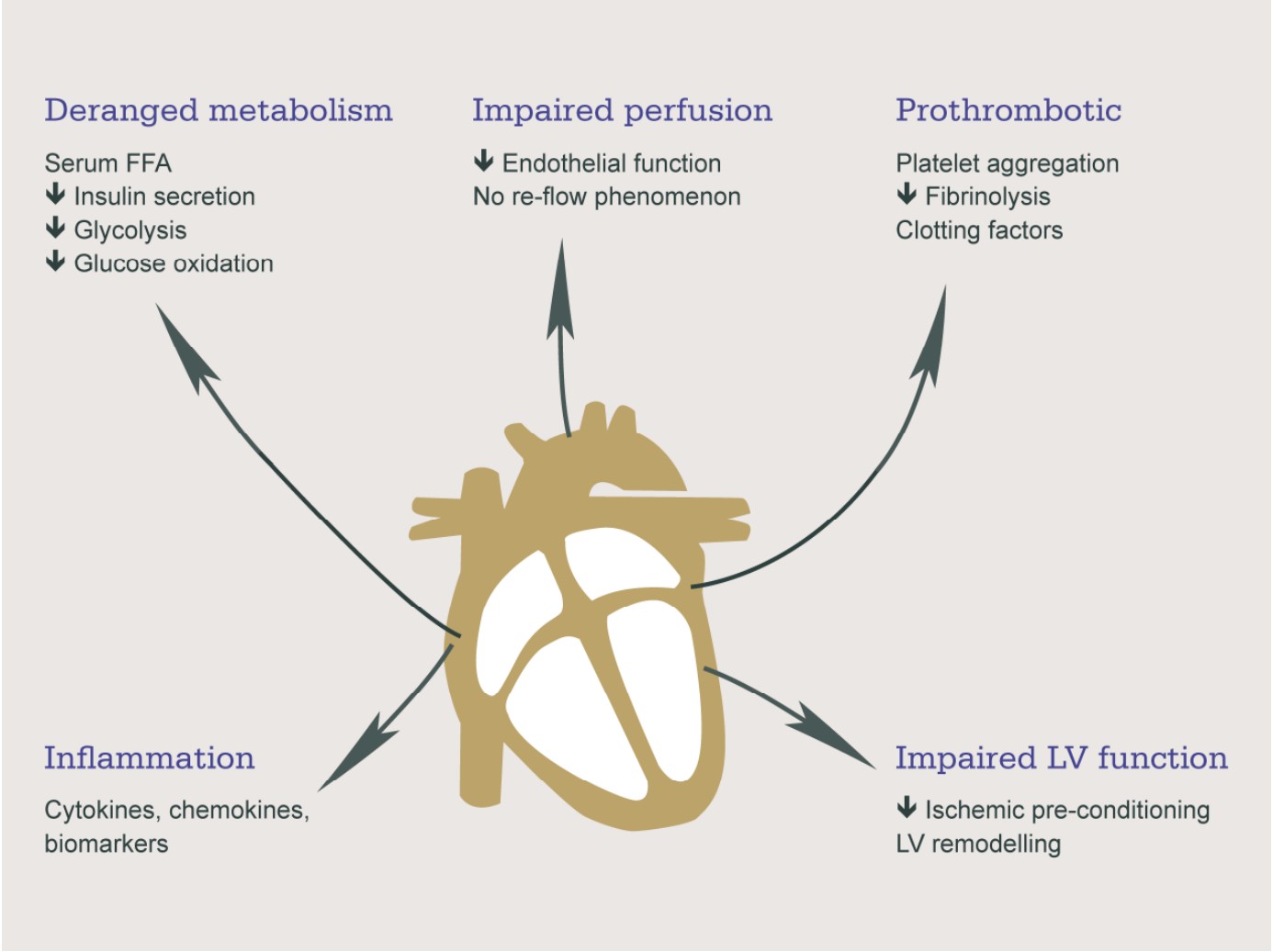
CAD by angiography N=363	None n=61	1 VD n=113	2 VD n=116	3 VD n=73
NGT	36 (59)	65 (57.9)	43 (37.1)	29 (39.7)
IGT	22 (36)	35 (30.9)	55 (47.1)*†	19 (26.0)*
Diabetes	3 (4.9)	13 (11.5)	18 (15.5)	23 (34)*†

Data are n(%).
*p<0.05 group 0 vs. respective value in groups 1, 2 ,and 3.
†p<0.05 group 1 vs. respective value in groups 2 and 3.
363 men submitted to OGTT and glucose disorders defined by WHO.

CAD: coronary artery disease.
IGT: impaired glucose tolerance.
NGT: normal glucose tolerance.
OGTT: oral glucose tolerance test.
VD: vessel disease.

Kowalska I, et al. *Diabetes Care*. 2001;24:897-901.

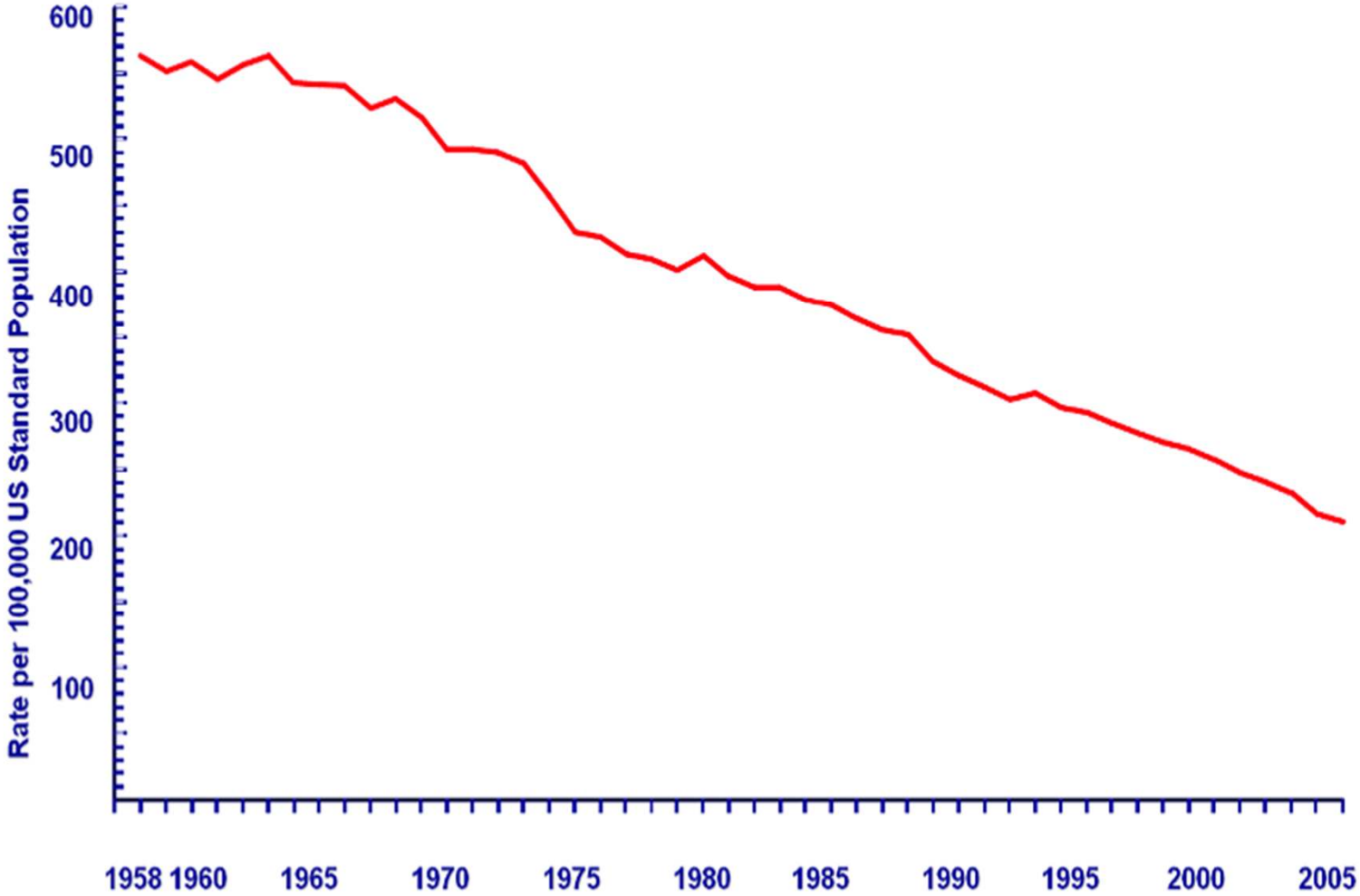
Cardiovascular consequences of glucose homeostasis abnormalities



FFA, free fatty acids. LV, left ventricular.

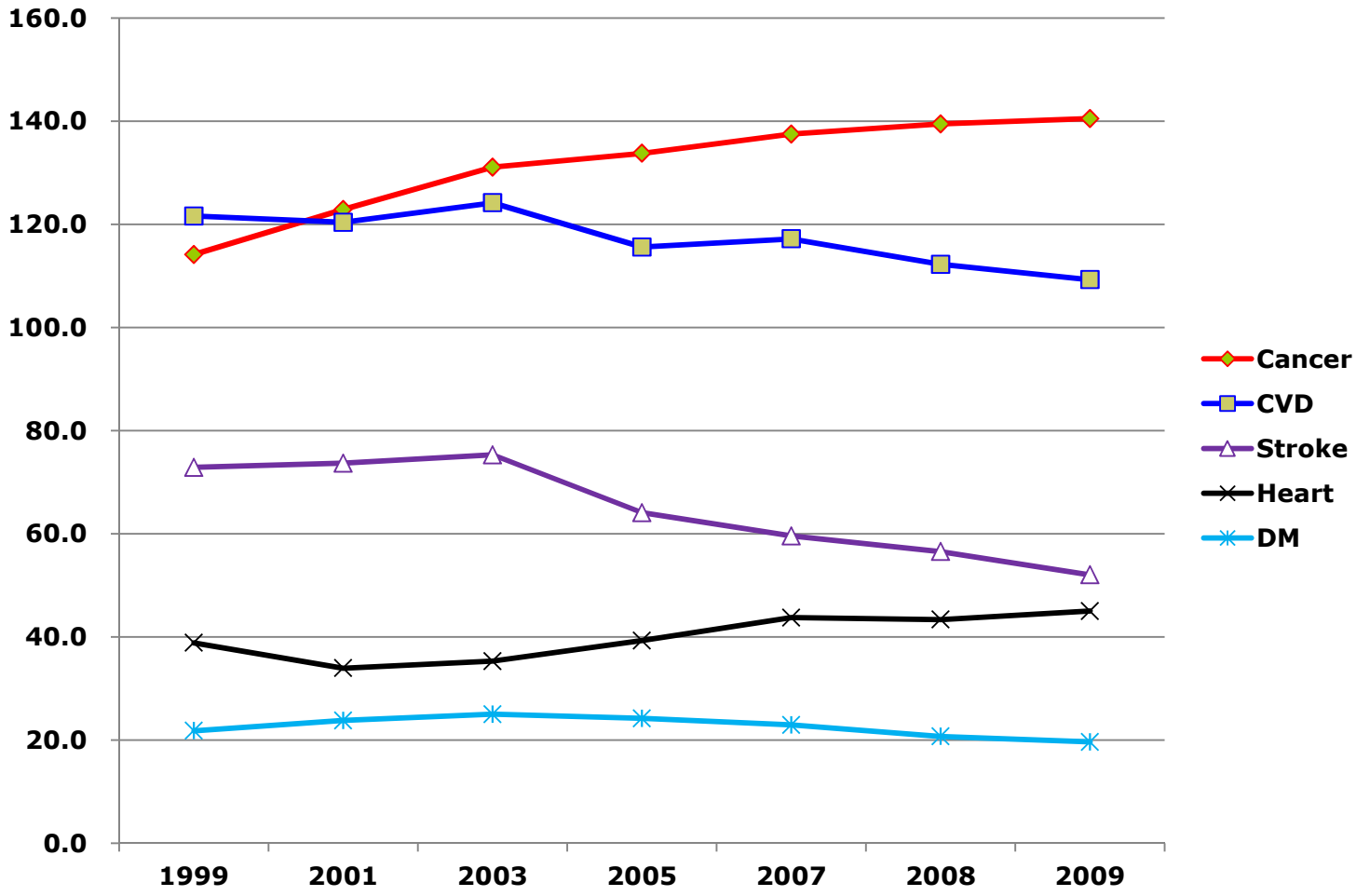
Zarich SW. *Rev Cardiovasc Med* 2006;7(suppl 2).S35-43.
Bauters C et al. *Eur Heart J* 2007;28:546-52.

Age-Adjusted Death Rates for CVD USA, 1958-2005



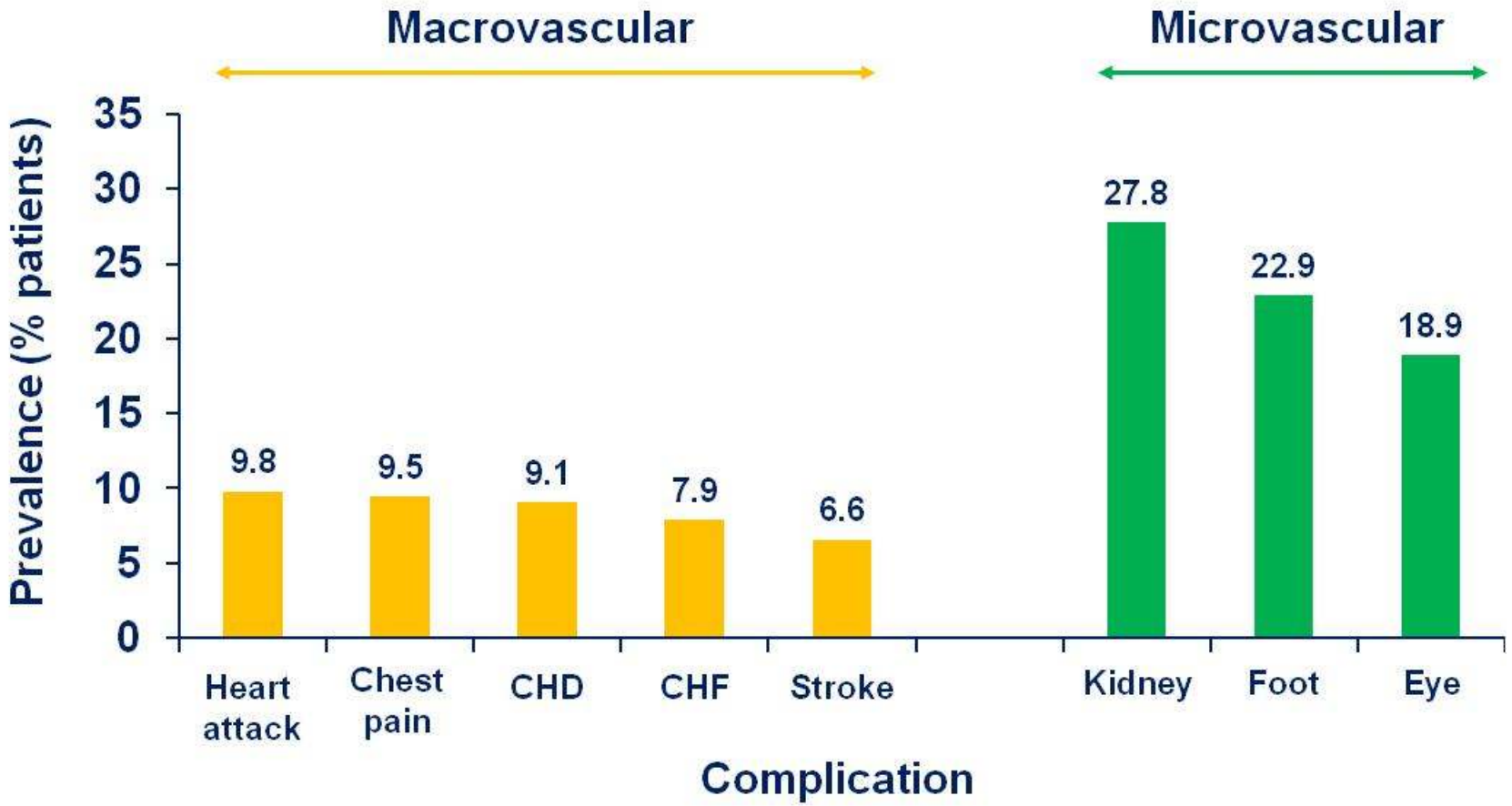
Source: CDC/NCHS, National Vital Statistics System, Mortality.

Cause of Death in Korea



통계청 URL:http://www.nso.go.kr

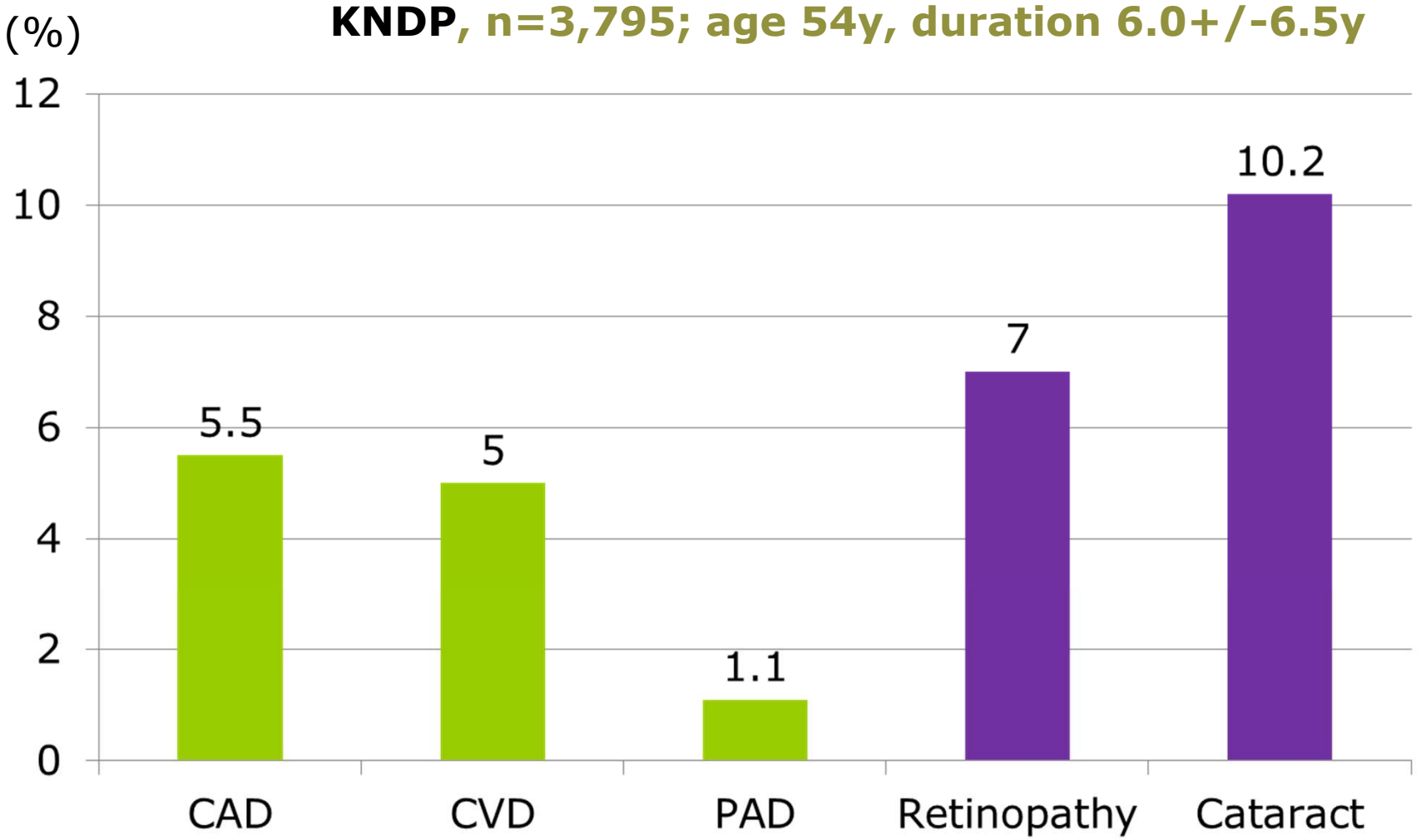
Macrovascular and microvascular complications occur frequently in people with diabetes



CHD = Coronary heart disease
CHF = Congestive heart failure

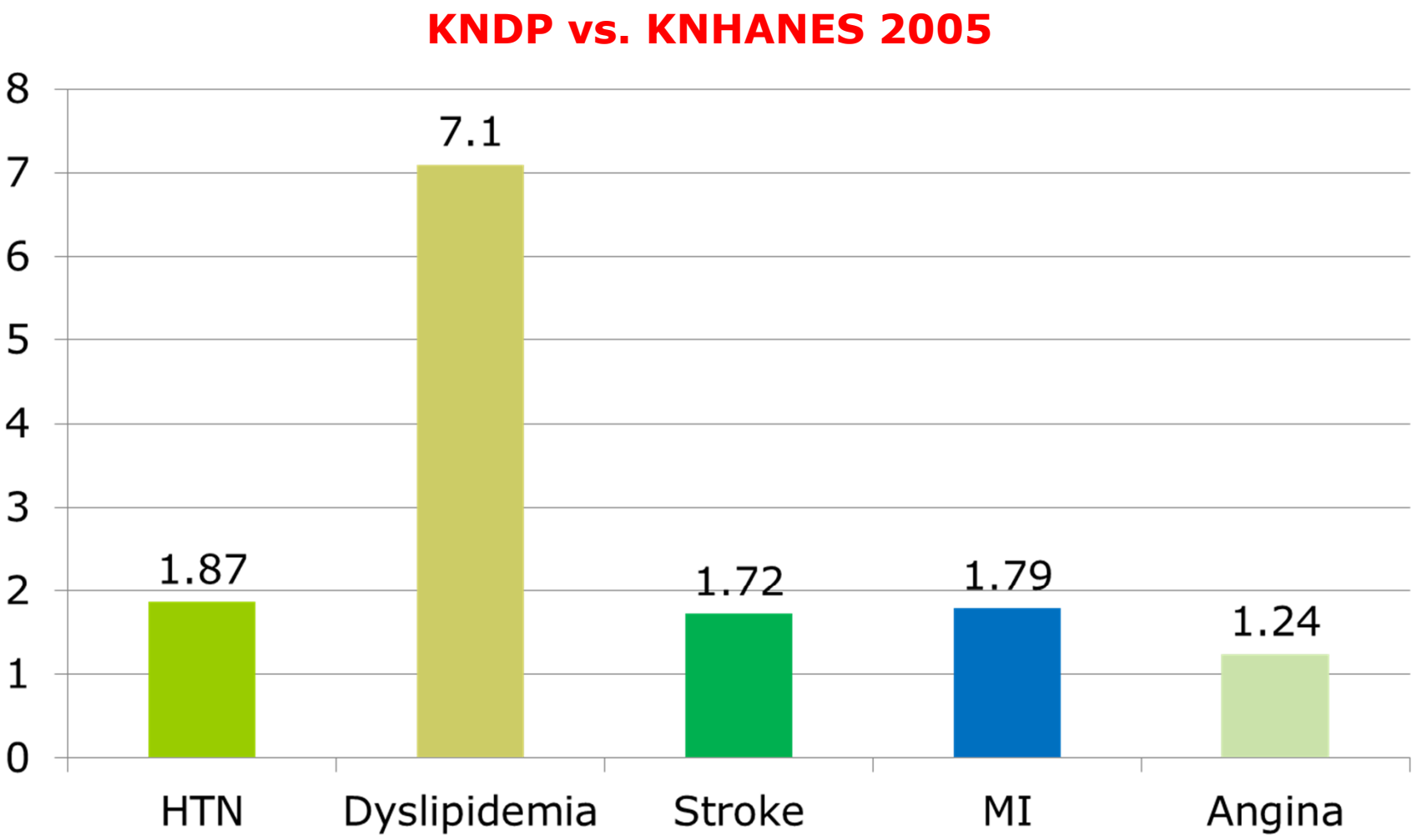
Deshpande AD, et *al.* *Phys Ther* 2008;88:1254–64.

Diabetes related complications in Korea



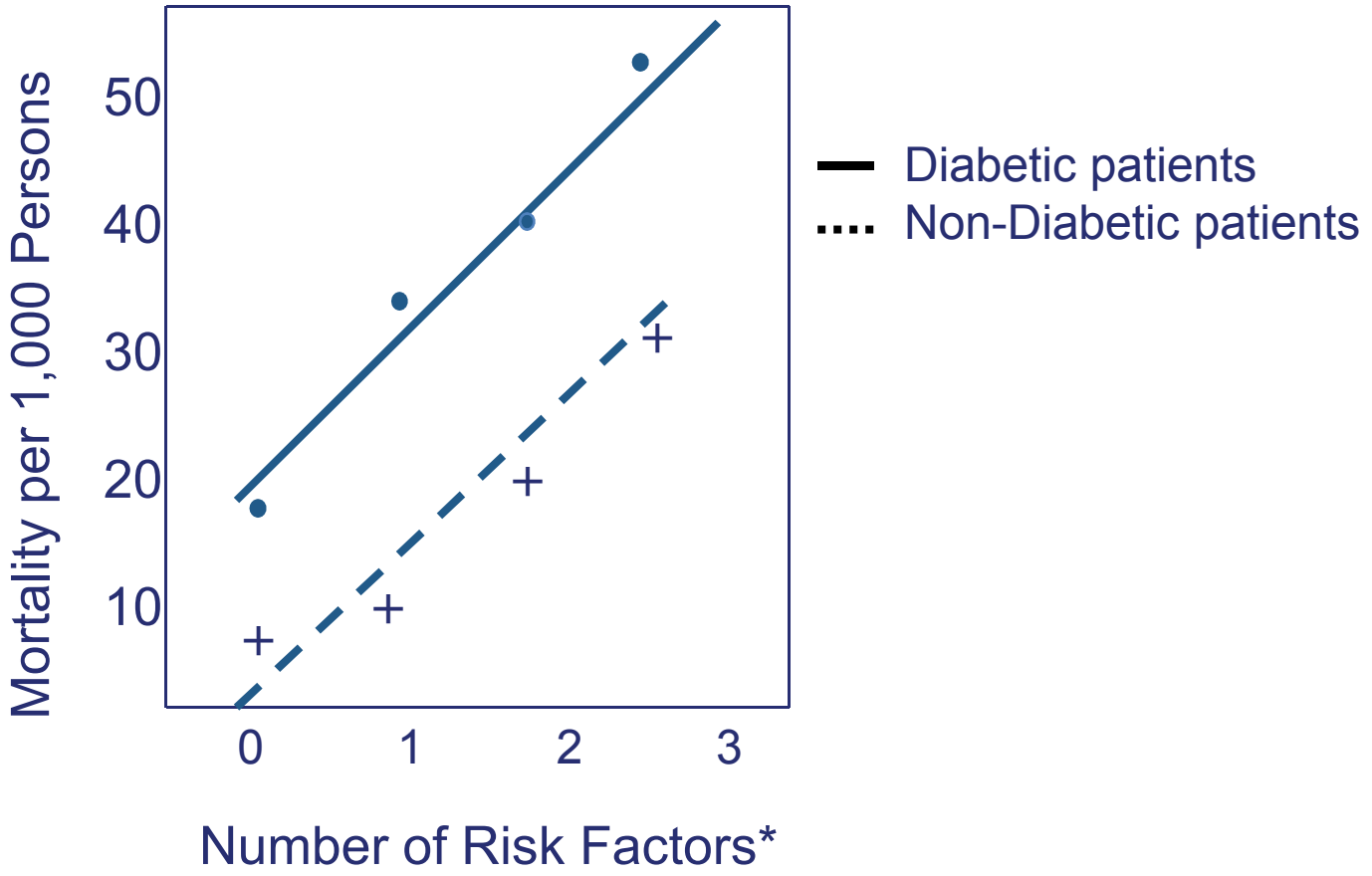
Diabetes Metab J 2011;35:504-512

Standardized prevalence ratio (SPR)



Diabetes Metab J 2011;35:504-512

Impact of Diabetes on Cardiovascular Mortality



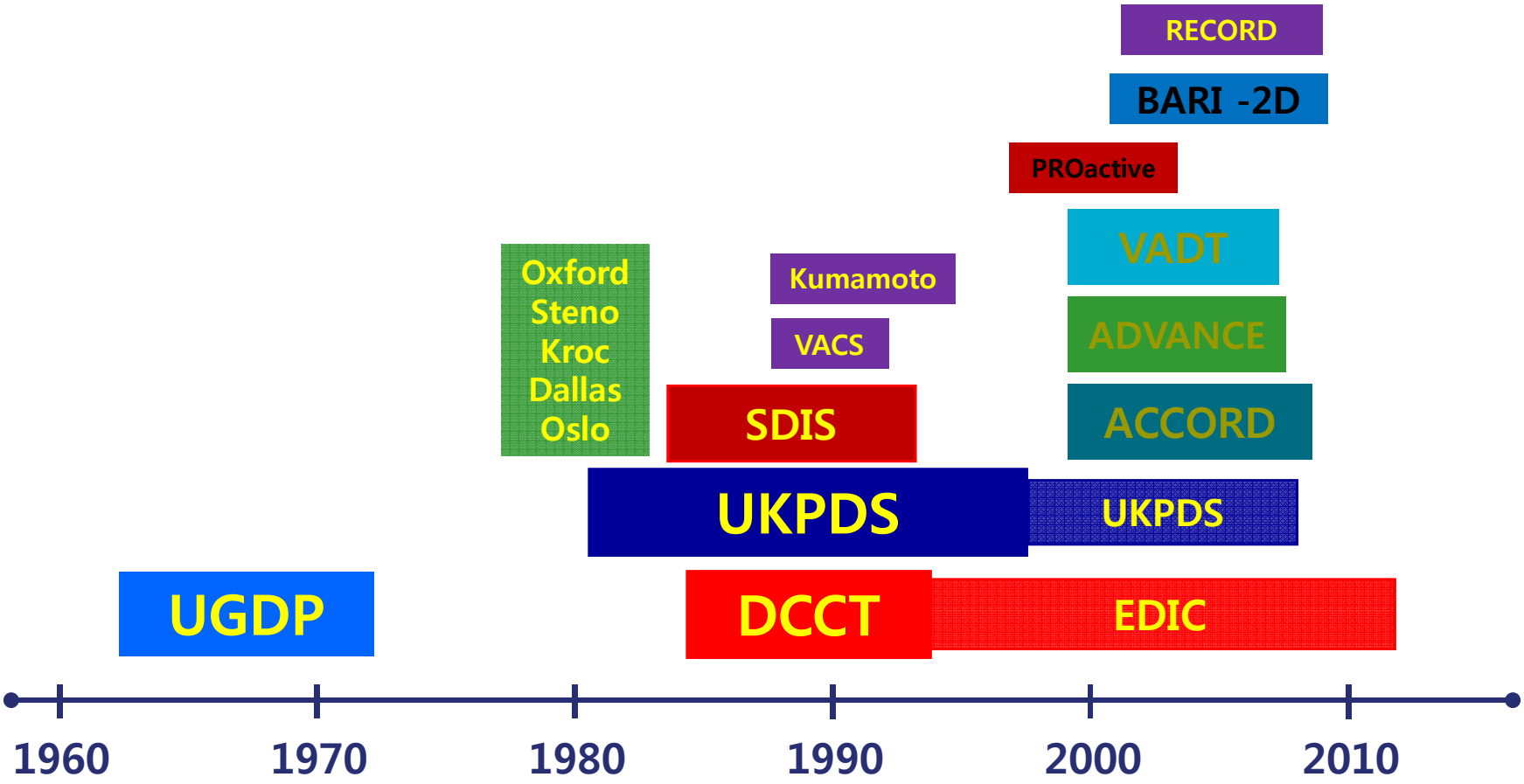
* Risk factors analyzed were smoking, dyslipidemia, and hypertension

ADA *Diabetes Care* 1989;12:573-9.

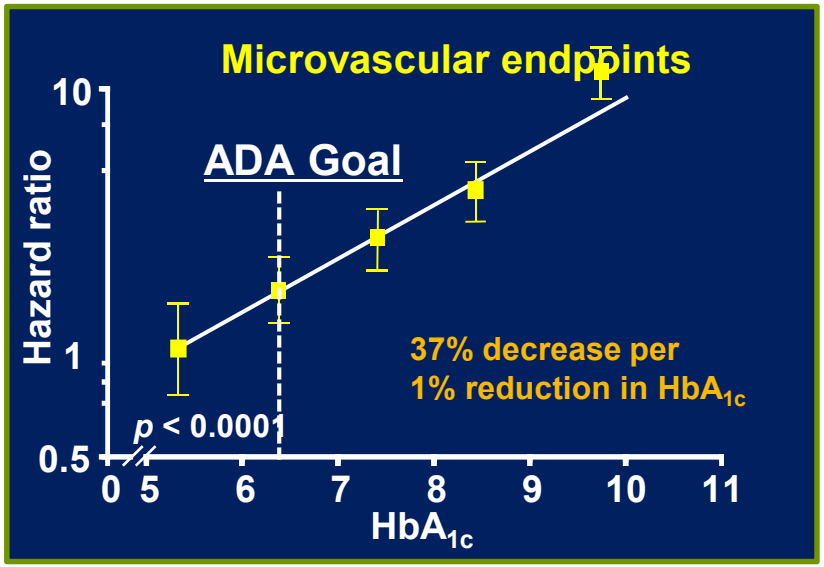
Rational for targeting normal glucose level

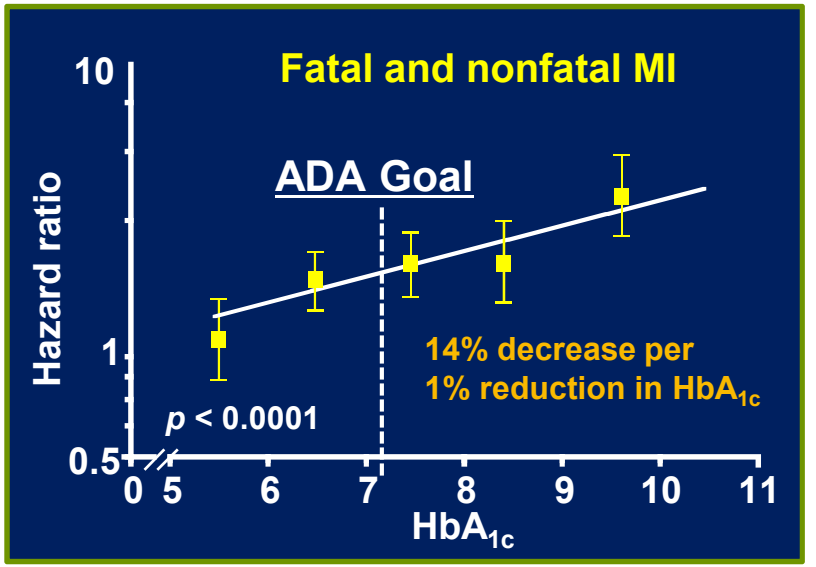
-Diabetic complications-

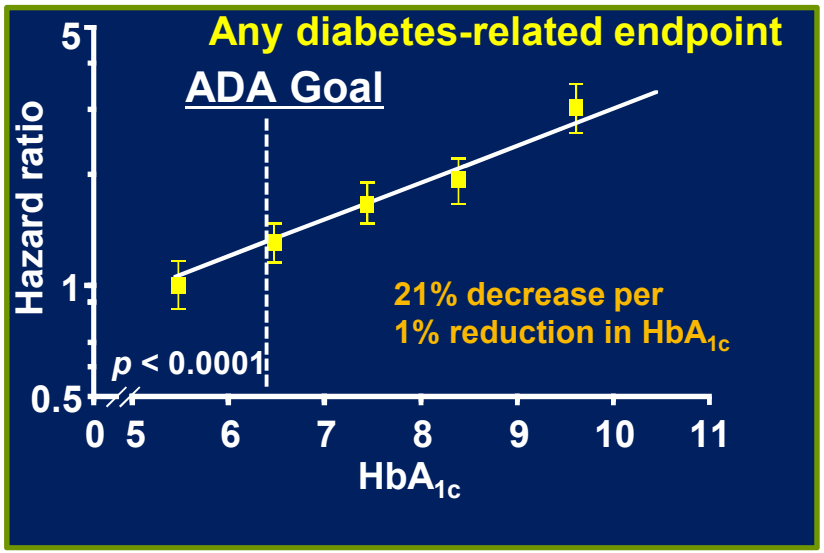
Landmark intervention trials in DM

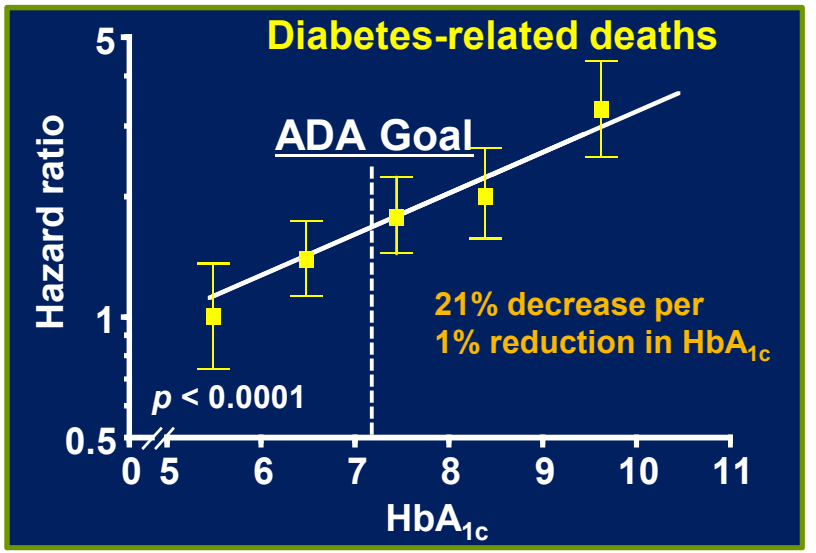


UKPDS epidemiological data: HbA_{1c} and risk of complications in T2DM



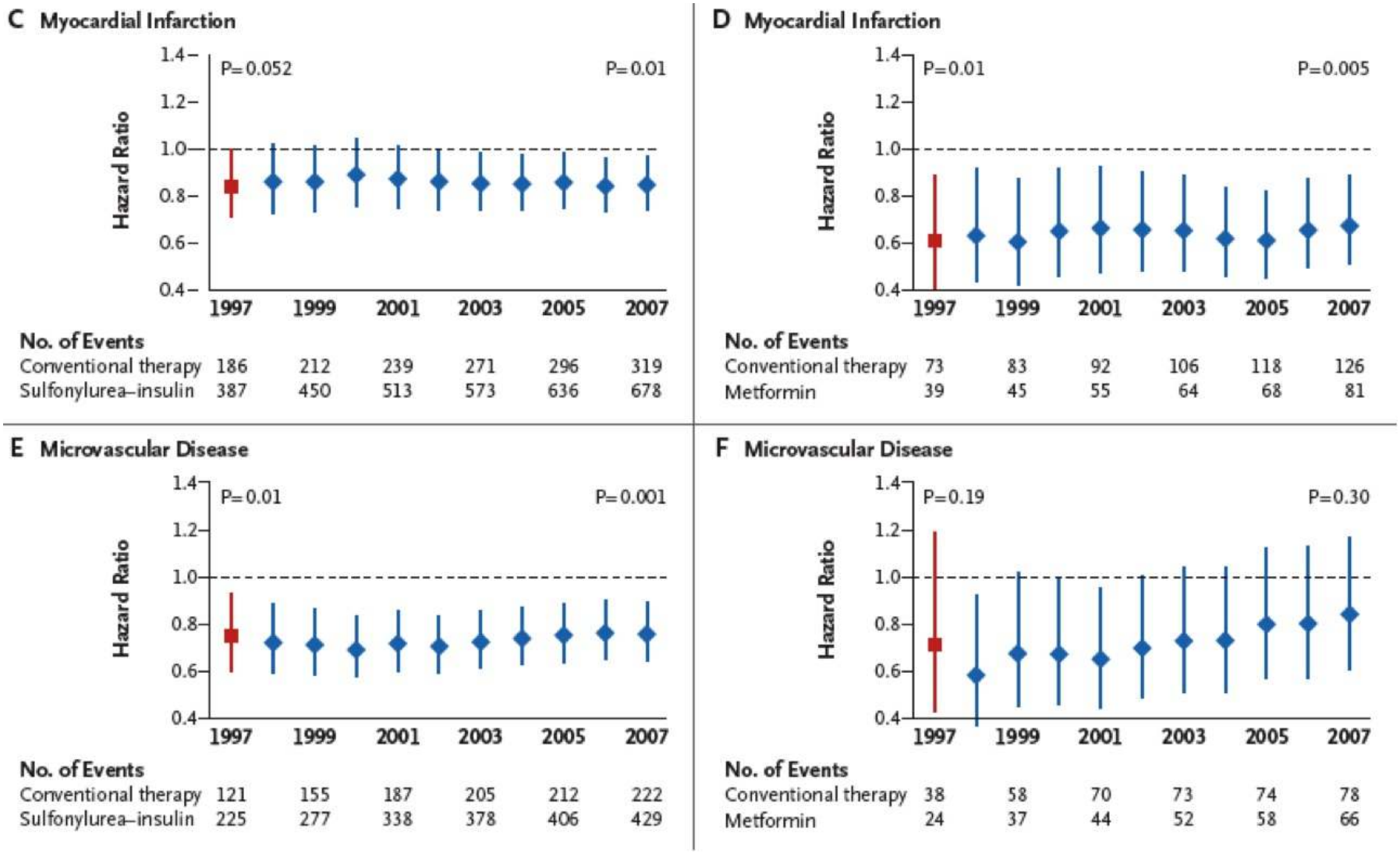






Stratton IM, *et al.* *BMJ* 2000;321:405–12.

10-year follow-up of UKPDS



Holmann RR et al. *NEJM 2009;*359:1577-1589

Legacy effect of early intensive intervention on blood glucose

After median 8.5 years post-trial follow-up in UKPDS

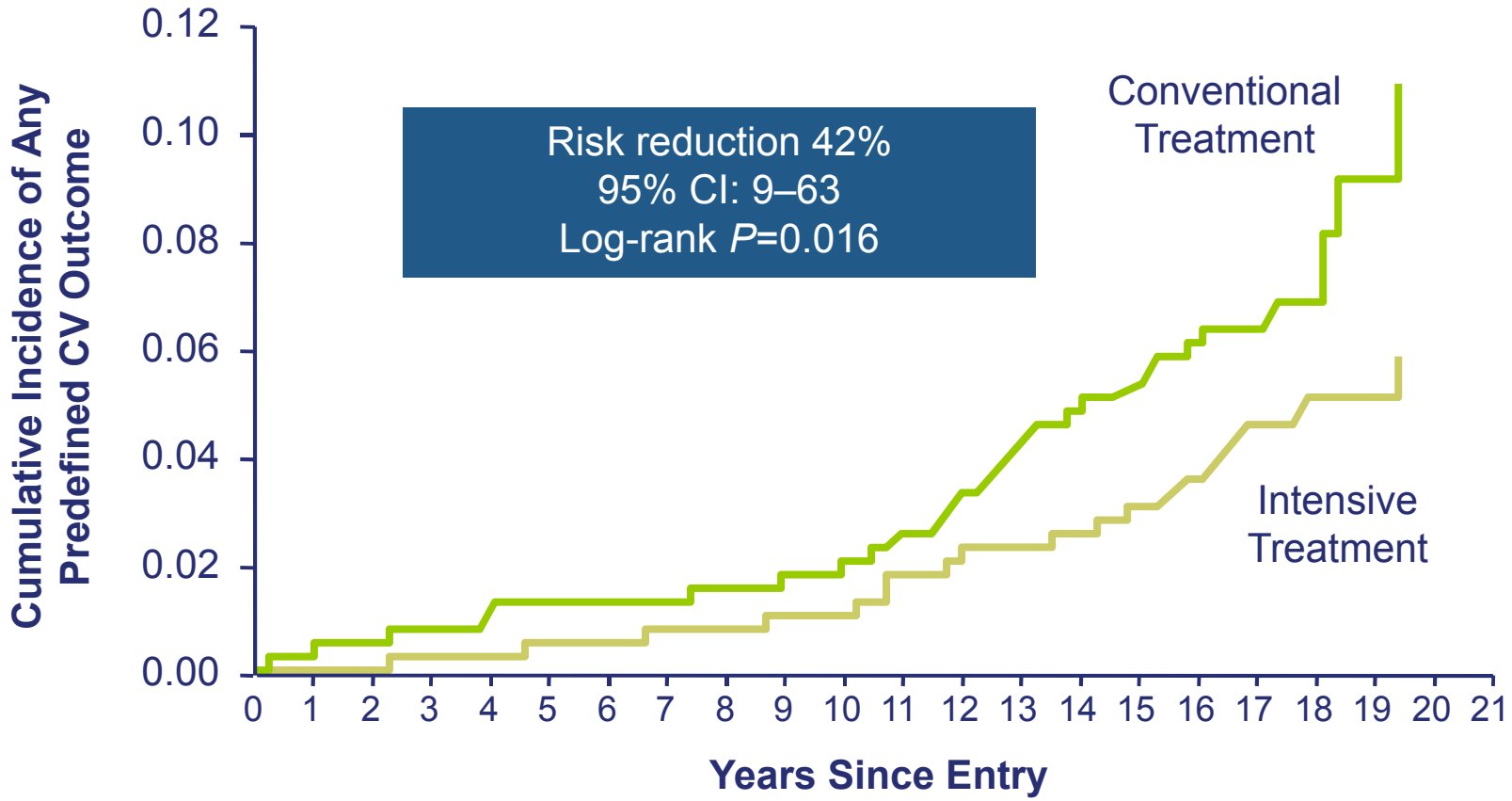
Aggregate endpoint		1997*	2007
Any diabetes related endpoint	*RRR:*	12%	9%
	p:	0.029	0.040
Microvascular disease	*RRR:*	25%	24%
	p:	0.0099	0.001
Myocardial infarction	*RRR:*	16%	15%
	p:	0.052	0.014
All-cause mortality	*RRR:*	6%	13%
	p:	0.44	0.007

RRR = Relative Risk Reduction, p = Log rank

***End of randomized intervention**

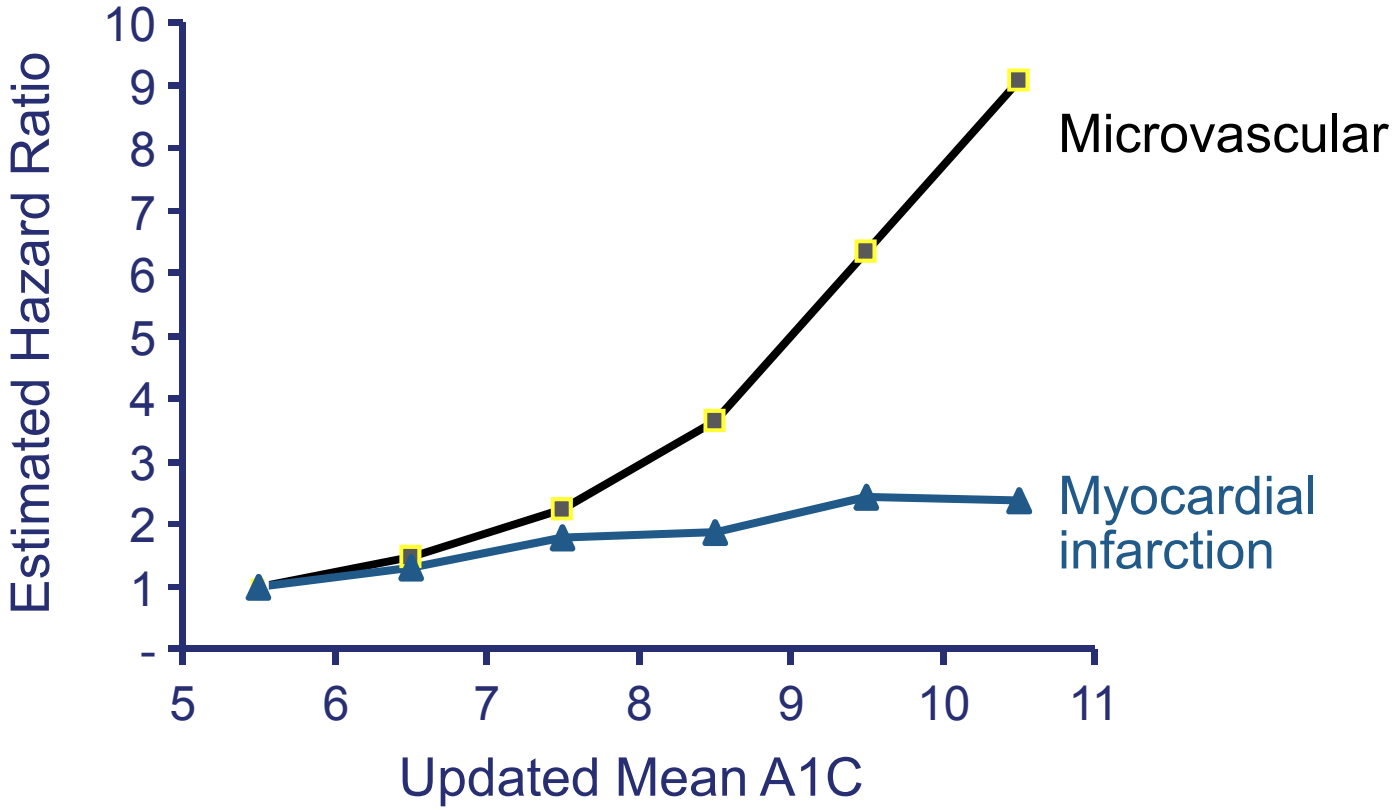
Holmann RR et al. *NEJM 2009;*359:1577-1589

DCCT/EDIC: Cumulative Incidence of the First of Any of the Predefined CVD Outcomes



Nathan DM *et al*. *N Engl J Med* 2005;353(25);2643-53.

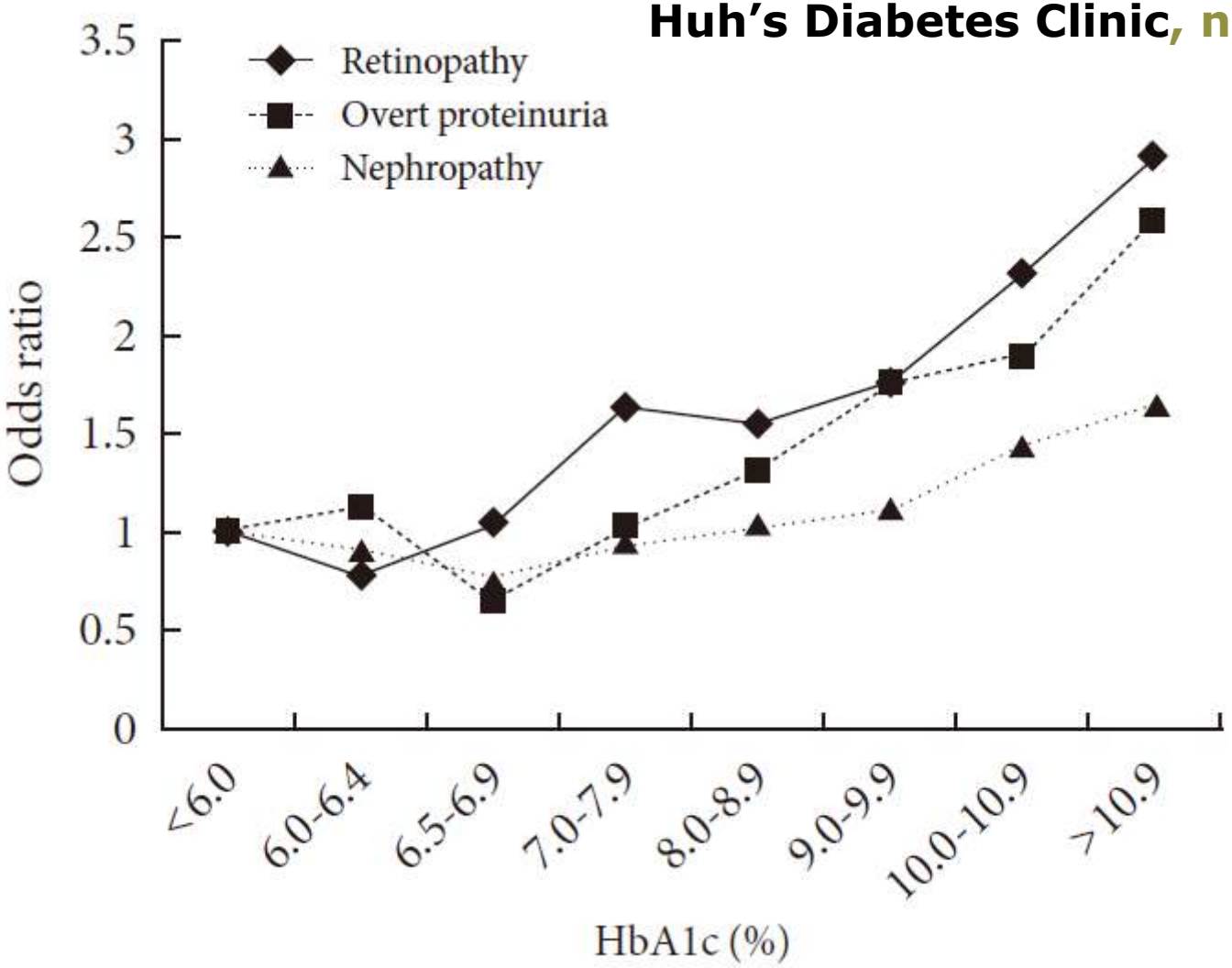
UKPDS: A1C As A Predictor of Micro- and Macrovascular Disease



Stratton IM *et al. BMJ.* 2000;321(7258):405-12.

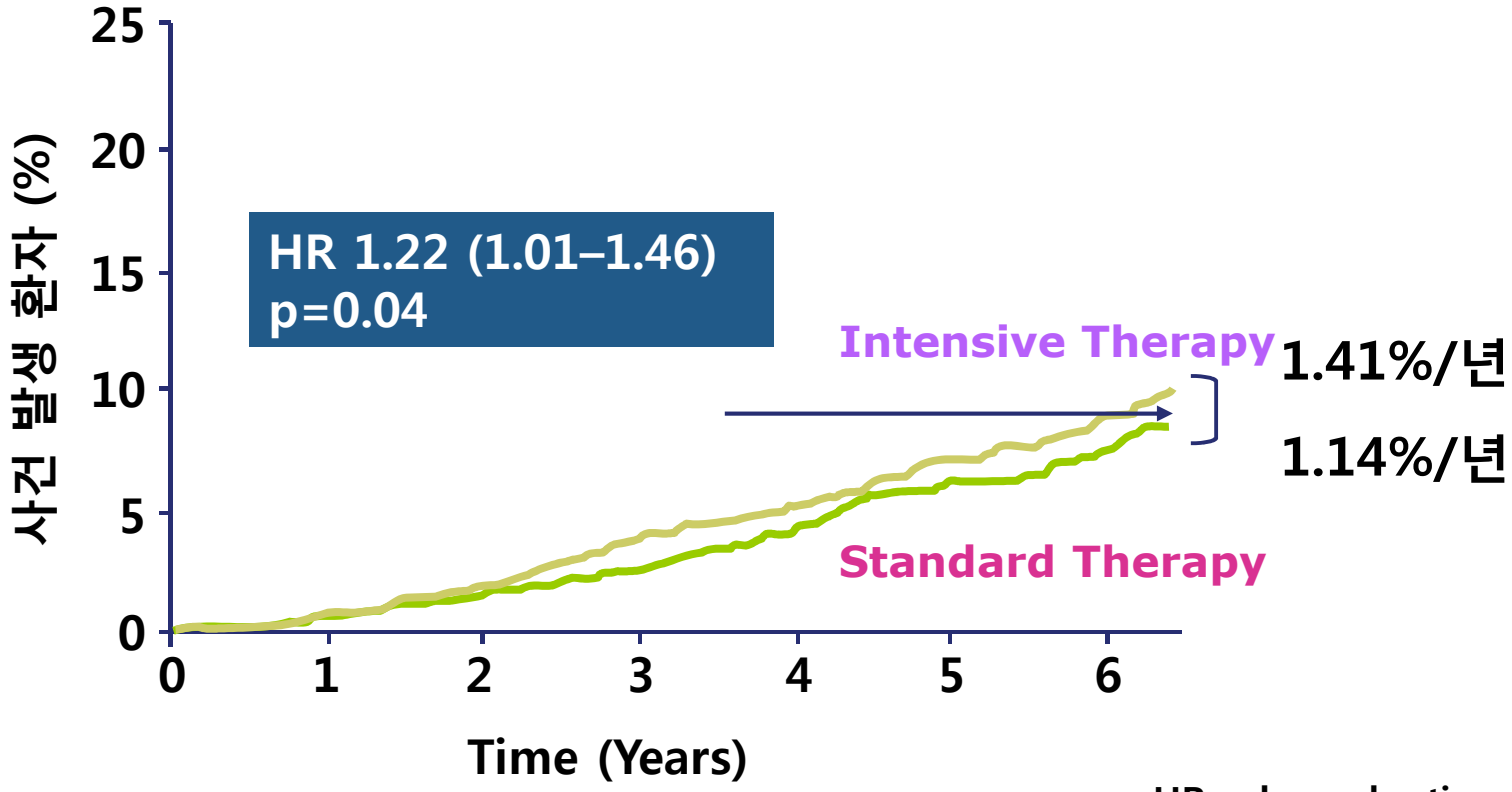
Glycemic control and Complications

Huh's Diabetes Clinic, n=8,198



Diabetes Metab J 2011;35:571-577

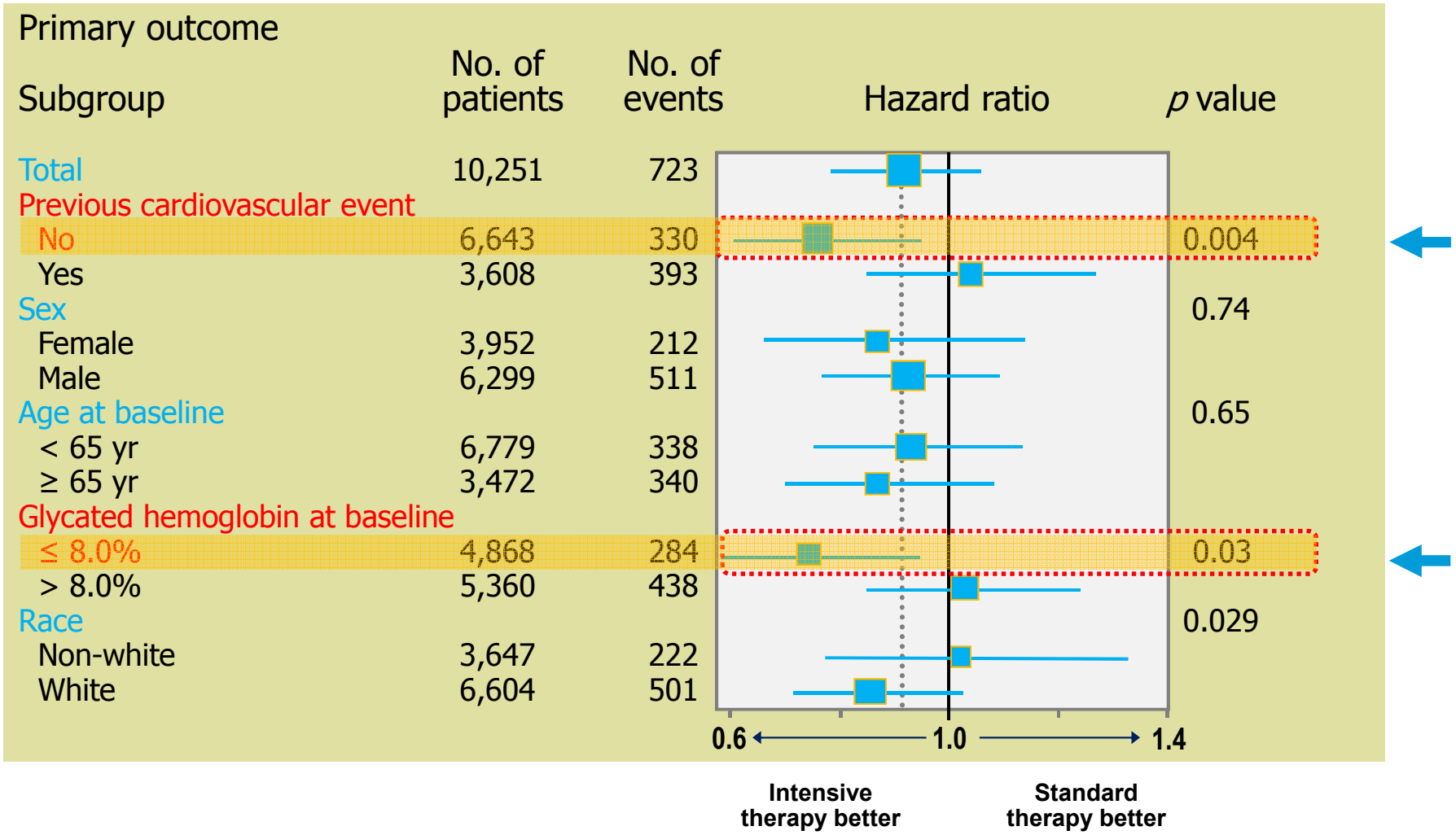
ACCORD: All-cause mortality



HR = hazard ratio

Gerstein HC *et al*. *N Engl J Med* 2008;358(24):2545-59

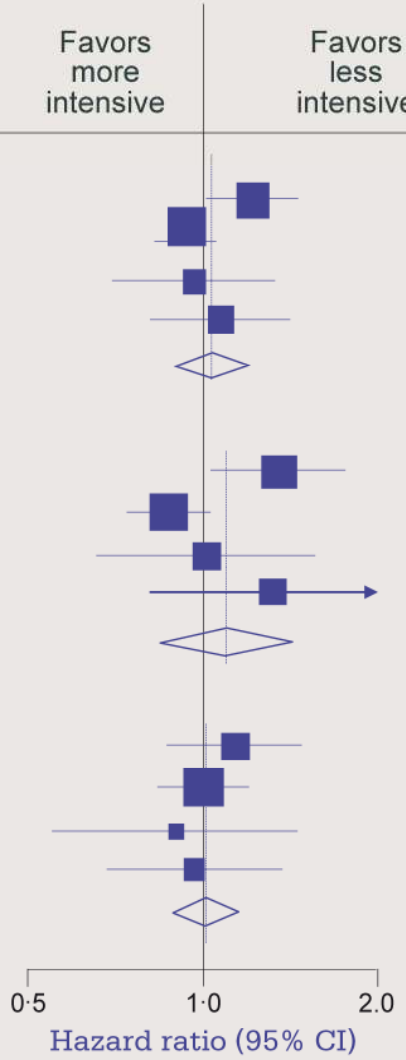
ACCORD: CVD outcomes



ACCORD. *N Engl J* Med 2008; 358:2545–59.

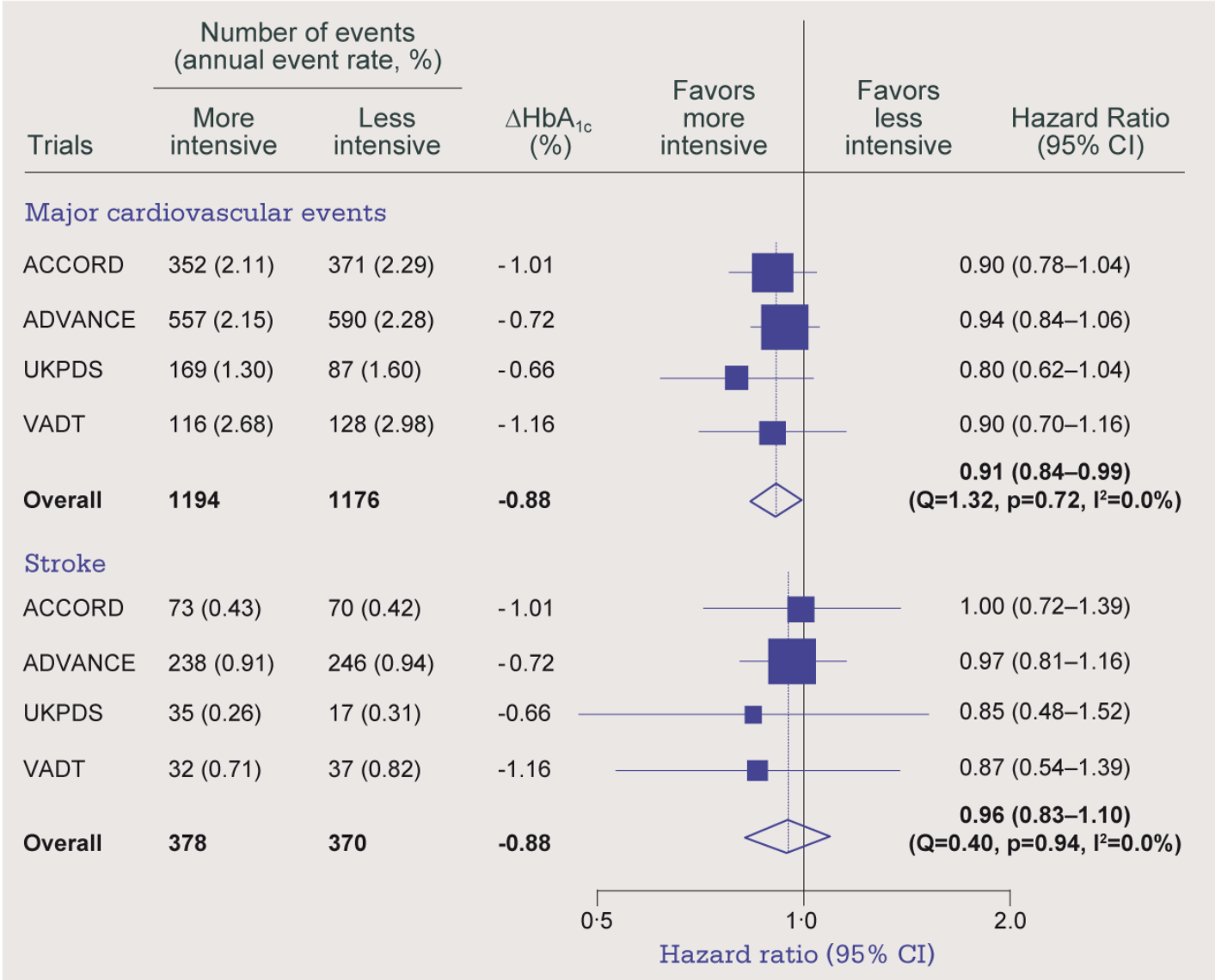
Meta-analysis from the CONTROL Group: Intensive glucose control and macrovascular outcomes in T2DM (1/3)

Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA$_{1c}$ (%)	Hazard Ratio (95% CI)
All-cause mortality				
ACCORD	257 (1.41)	203 (1.14)	-1.01	1.22 (1.01–1.46)
ADVANCE	498 (1.86)	533 (1.99)	-0.72	0.93 (0.83–1.06)
UKPDS	123 (0.13)	53 (0.25)	-0.66	0.96 (0.70–1.33)
VADT	102 (2.22)	95 (2.06)	-1.16	1.07 (0.81–1.42)
Overall	**980**	**884**	**-0.88**	**1.04 (0.90–1.20)** **(Q=5.71, p=0.13, I^2=47.5%)**
Cardiovascular death				
ACCORD	135 (0.79)	94 (0.56)	-1.01	1.35 (1.04–1.76)
ADVANCE	253 (0.95)	289 (1.08)	-0.72	0.88 (0.74–1.04)
UKPDS	71 (0.53)	29 (0.52)	-0.66	1.02 (0.66–1.57)
VADT	38 (0.83)	29 (0.63)	-1.16	1.32 (0.81–2.14)
Overall	**497**	**441**	**-0.88**	**1.10 (0.84–1.42)** **(Q=8.61, p=0.04, I^2=65.1%)**
Non-cardiovascular death				
ACCORD	115 (0.63)	98 (0.55)	-1.01	1.14 (0.87–1.49)
ADVANCE	245 (0.92)	244 (0.91)	-0.72	1.00 (0.84–1.20)
UKPDS	52 (0.39)	24 (0.43)	-0.66	0.90 (0.55–1.46)
VADT	64 (1.40)	66 (1.43)	-1.16	0.97 (0.69–1.36)
Overall	**476**	**432**	**-0.88**	**1.02 (0.89–1.18)** **(Q=0.99, p=0.80, I^2=0.0%)**



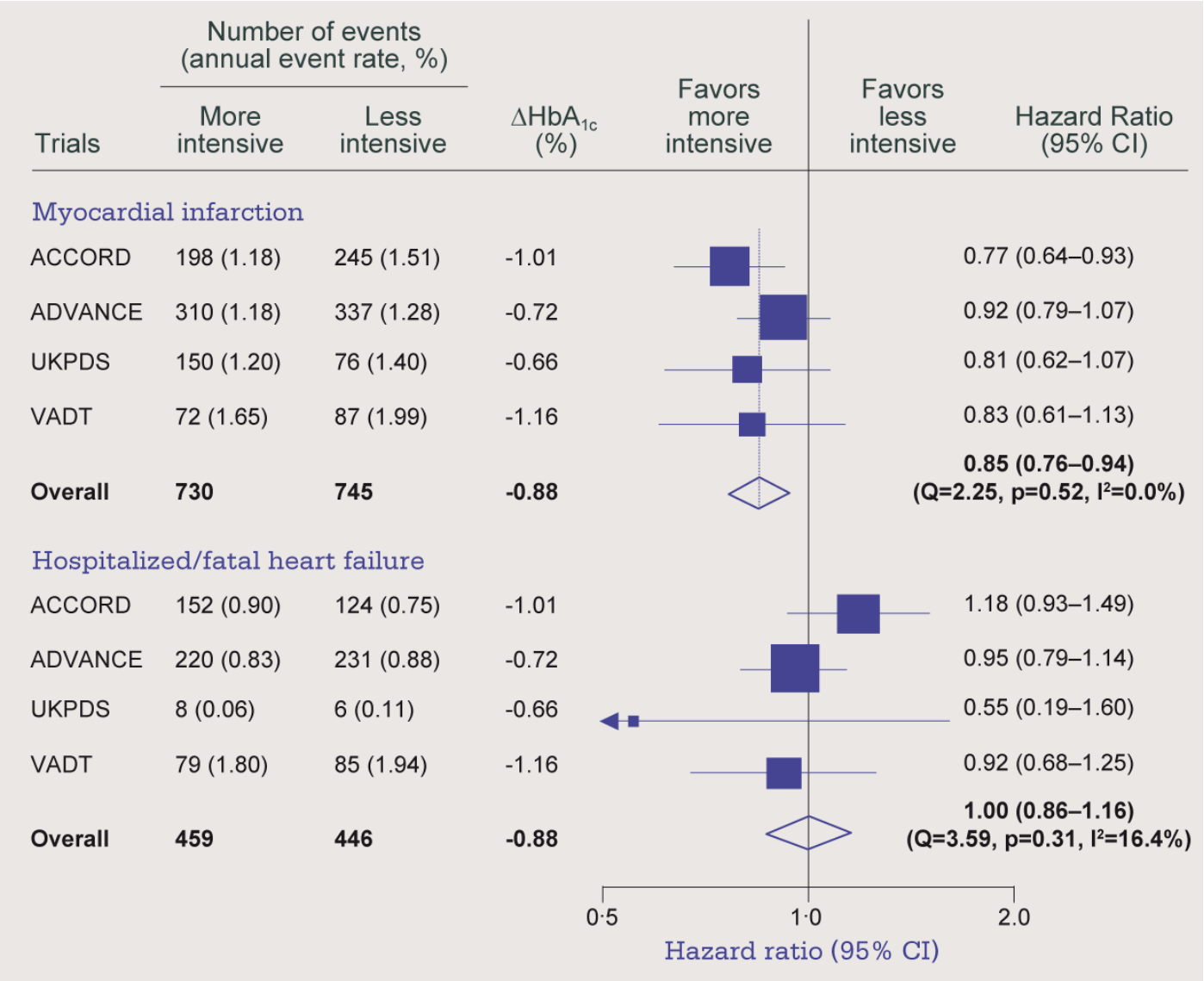
Turnbull FM, et al. *Diabetologia* 2009;52:2288-98.

Meta-analysis from the CONTROL Group: Intensive glucose control and macrovascular outcomes in T2DM (2/3)



Turnbull FM, et al. *Diabetologia* 2009;52:2288-98.

Meta-analysis from the CONTROL Group: Intensive glucose control and macrovascular outcomes in T2DM (3/3)



Turnbull FM, et al. *Diabetologia* 2009;52:2288-98.

Glycemic control and CVD in Diabetes

Study	Microvascular		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT/ EDIC	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Initial Trial

Long-term F/U

혈당조절에 의한 심혈관 질환 위험 감소를 입증하기 어려운 이유는?

- (혈당 조절을 하면서) 심혈관 질환의 절대적 위험이 줄어들므로, 따라서
  - 많은 수의 피험자가 필요
  - 장기간 추적관찰해야 하며, 치료법 변경에 대해 추적관찰 해야 함
- 당뇨병이 너무 진전되었을 때 혈당 조절 시작

Rational for “why insulin?” to target normal glucose level

Research on the impact of insulin use on MI (ROLE-MI study)

Objective

- To determine whether the rate of subsequent MI differs in patients with T2DM newly initiated on insulin glargine or NPH

Data source

- Integrated Health Care Information System (IHCIS) national managed care database

Patients

- Newly initiated on insulin glargine (*n* = 14,730) or NPH (*n* = 5,461) between March 2001 and February 2005
- Failed OADs (on OADs during 6 months prior to insulin initiation)
- Had continuous health plan enrollment for at least 6 months prior to, and 12 months following, insulin initiation
- Followed for up to 5 years with an average follow-up of 2 years

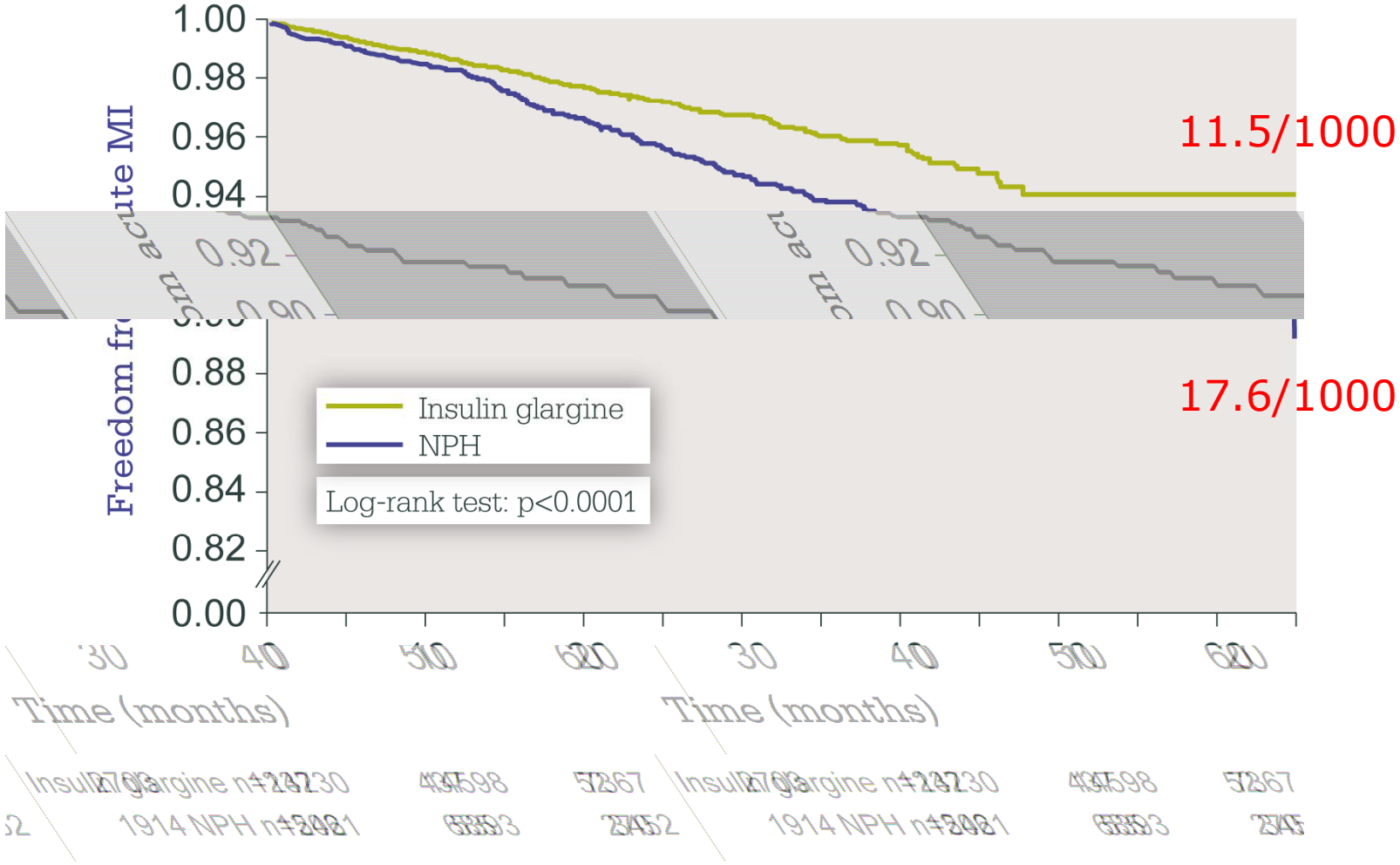
Rhoads GG, et al. *Am J Cardiol* 2009;104:910-6.

Research on the impact of insulin use on MI (ROLE-MI study)

	Glargine (n=14,730)	NPH (n=5,461)	p
Age	56.2	55.8	0.025
Women	44.2%	50.3%	<0.001
Hypertension	56.7%	52.3%	<0.001
Hyperlipidemia	51.0%	41.7%	<0.001
MI	3.4%	4.5%	0.001
Stroke	5.7%	6.5%	0.039
HbA1C	9.28%	8.91%	<0.0001
Creatinine	1.07	1.11	NS
LDLC	102	104	NS
TG	240	221	NS
HDLC	45.7	46.1	NS

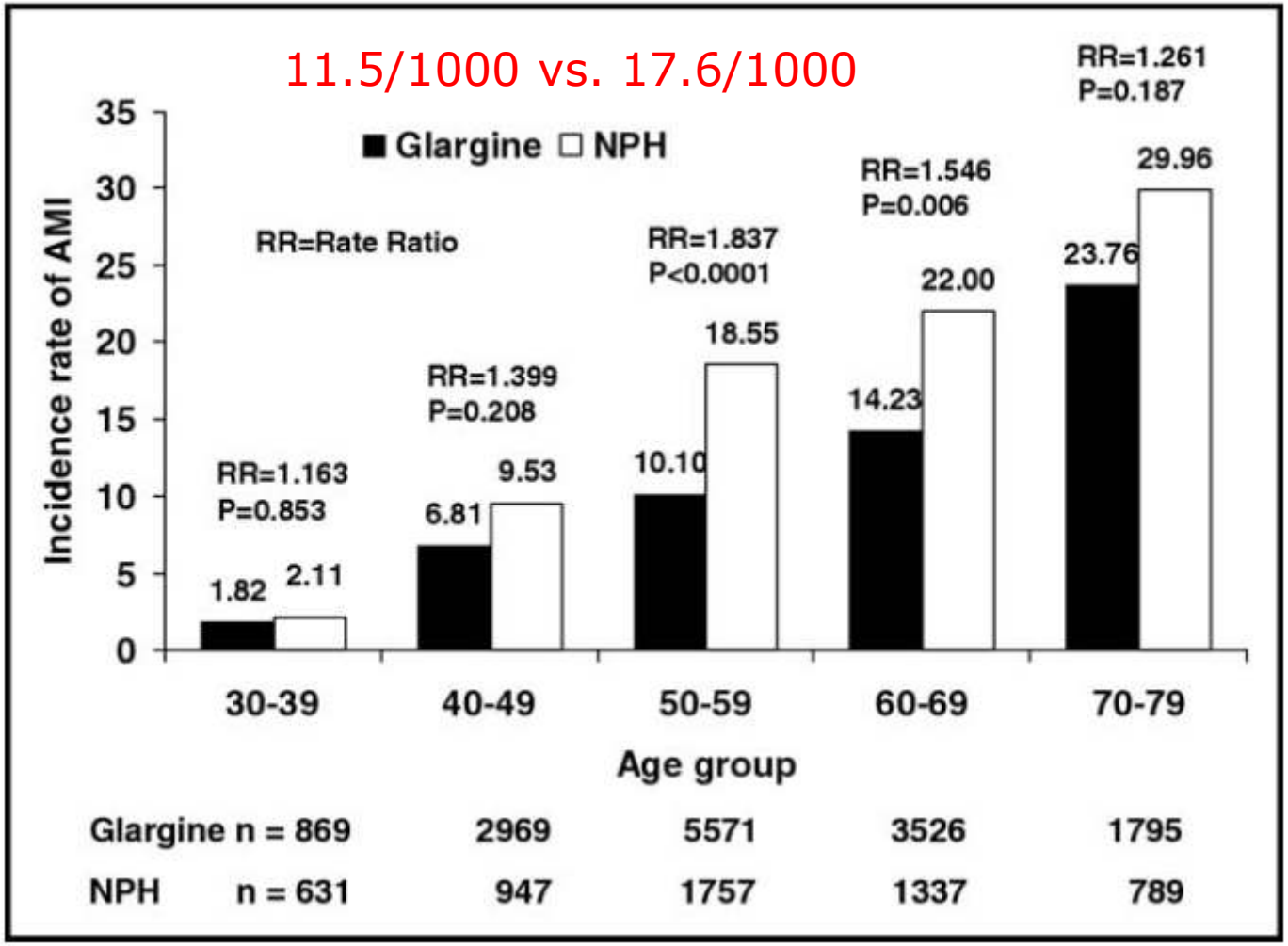
Rhoads GG, et al. *Am J Cardiol* 2009;104:910-6.

MI risk with insulin glargine vs NPH: Retrospective US database analysis



Rhoads GG, et al. *Am J Cardiol* 2009;104:910-6.

MI risk with insulin glargine vs NPH: Retrospective US database analysis



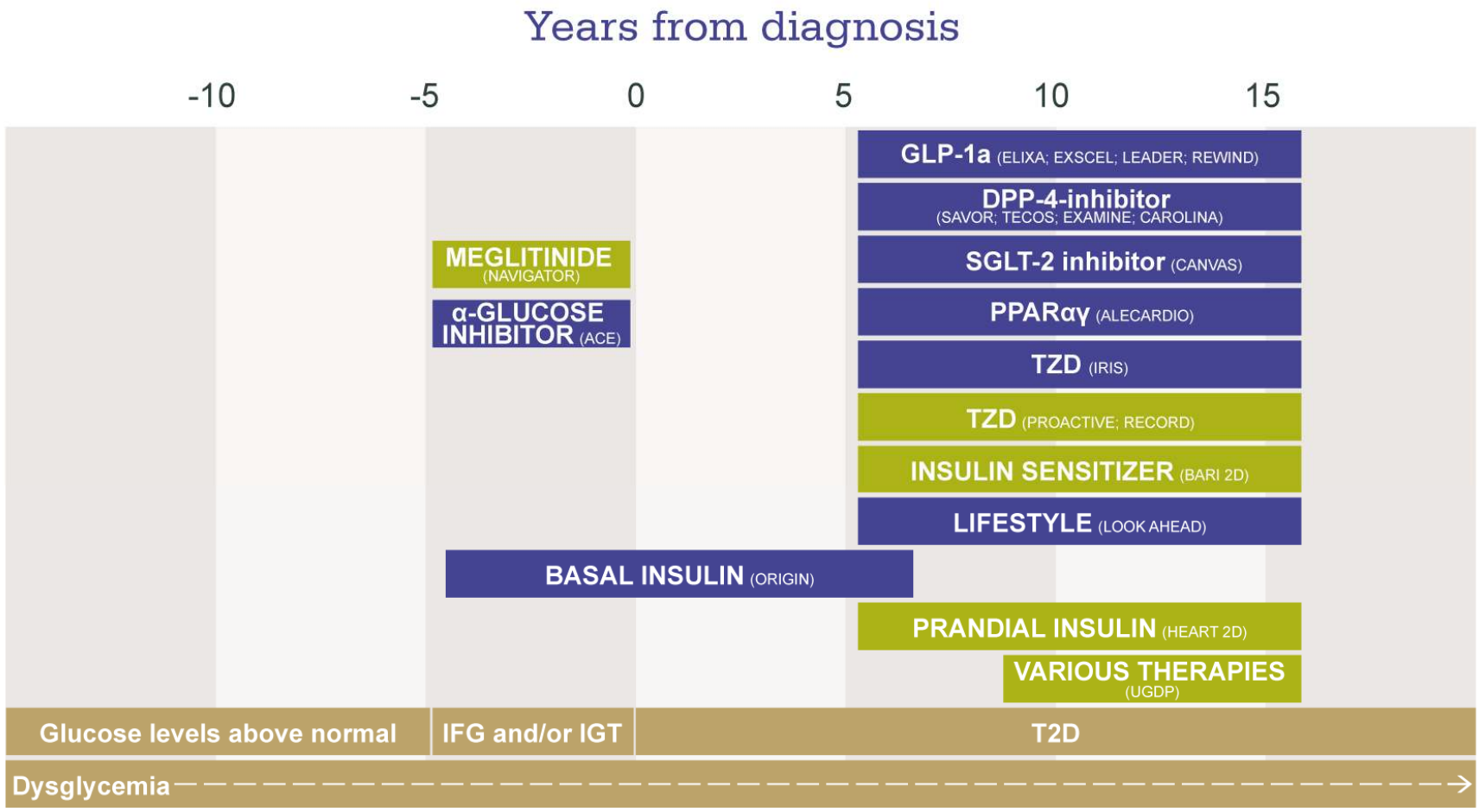
Rhoads GG, et al. *Am J Cardiol* 2009;104:910-6.

Why Glargine was better than NPH?

- Glycemic control
  - HbA1C : Glargine 8.15% vs. NPH 8.11%
- Hypoglycemia
  - Greater rate of medical claims for hypoglycemia in NPH insulin than Glargine
- Effects on IGF axis and oxidative stress
  - NPH was associated with lower IGF-1 levels than insulin glargine
  - Low IGF-1 was predictor of IHD
  - Exogenous IGF-1 decrease inflammation, oxidative stress and atherosclerosis

Rhoads GG, et al. *Am J Cardiol* 2009;104:910-6.

Outcomes trials evaluating individual treatments for patients with dysglycemia

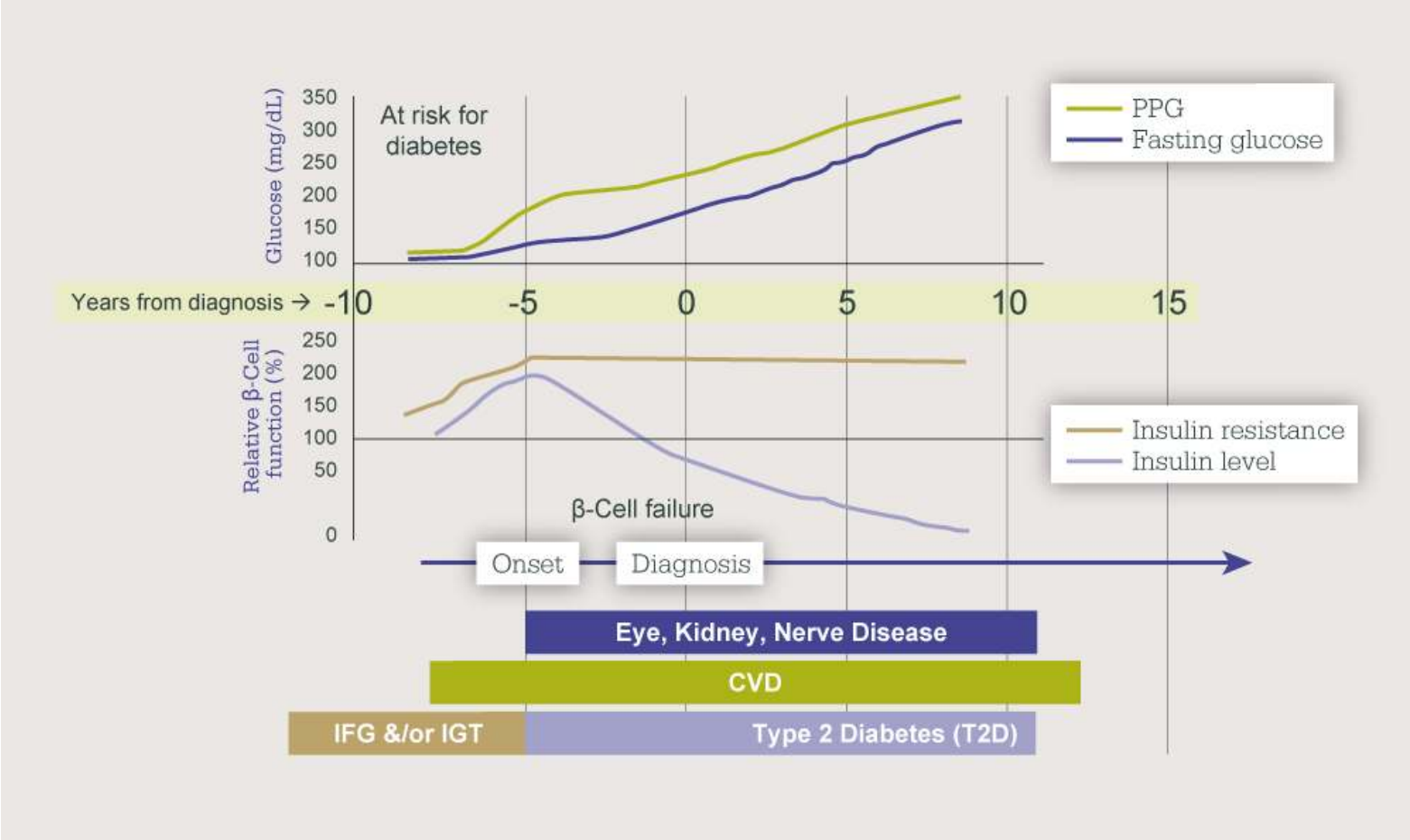


Completed trials
Ongoing trials

The trials are shown in relation to the eligibility criteria, with respect to diabetes duration at randomization.

Adapted from Gerstein, HC. Nat Rev Endocrinol 2009;5:270–275.

In individuals with dysglycemia, there is an early relative deficiency in insulin, even at early stage



Bergenstal R et al. In: DeGroot L, Jameson J, eds. *Endocrinology*. 4th ed. Philadelphia, Pa: W.B. Saunders Company; 2001:821.

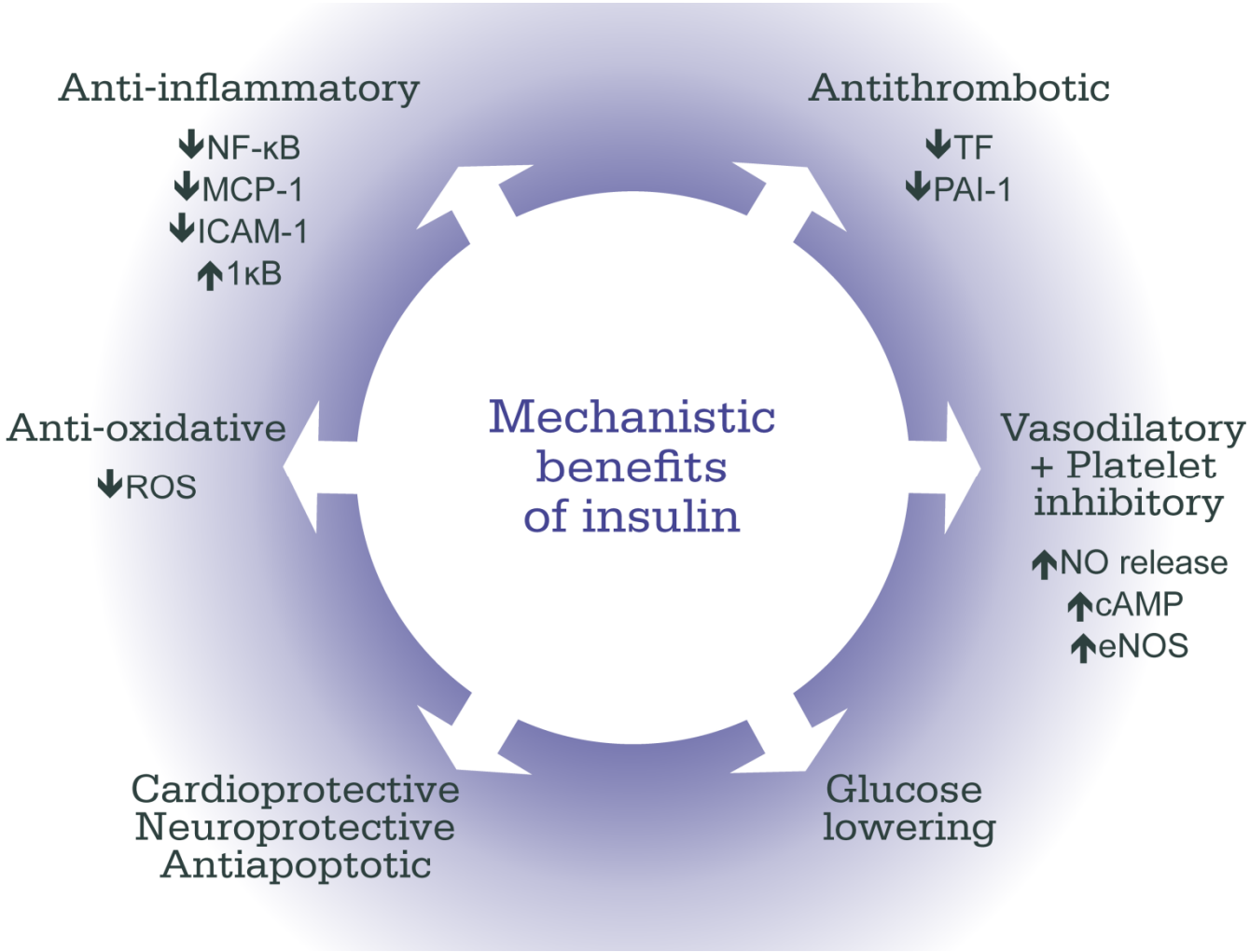
High glucose and CV risk

- Excess glucose may directly harm vascular endothelium and other tissues
- Reduced insulin promotes mobilization of FFA from adipose tissue
  - Reduce HDL, increase LDL
  - Increase insulin resistance at liver and muscle
  - Damage insulin secreting beta cells
  - Promote arrhythmia in response to ischemia
  - Activate cellular inflammatory process

Gerstein HC, et al. *Am Heart J* 2008;155:26-32.

Potential CV beneficial effects of replacing insulin in dysglycemic individuals

- CV parameters such as lipids, platelet function, inflammatory markers, endothelial function might improve with insulin replacement therapy



Adapted from Dandona P, et al. *Am J Cardiol* 2007;99(suppl):15B-26.

Outcome Reduction with Initial Glargine Intervention

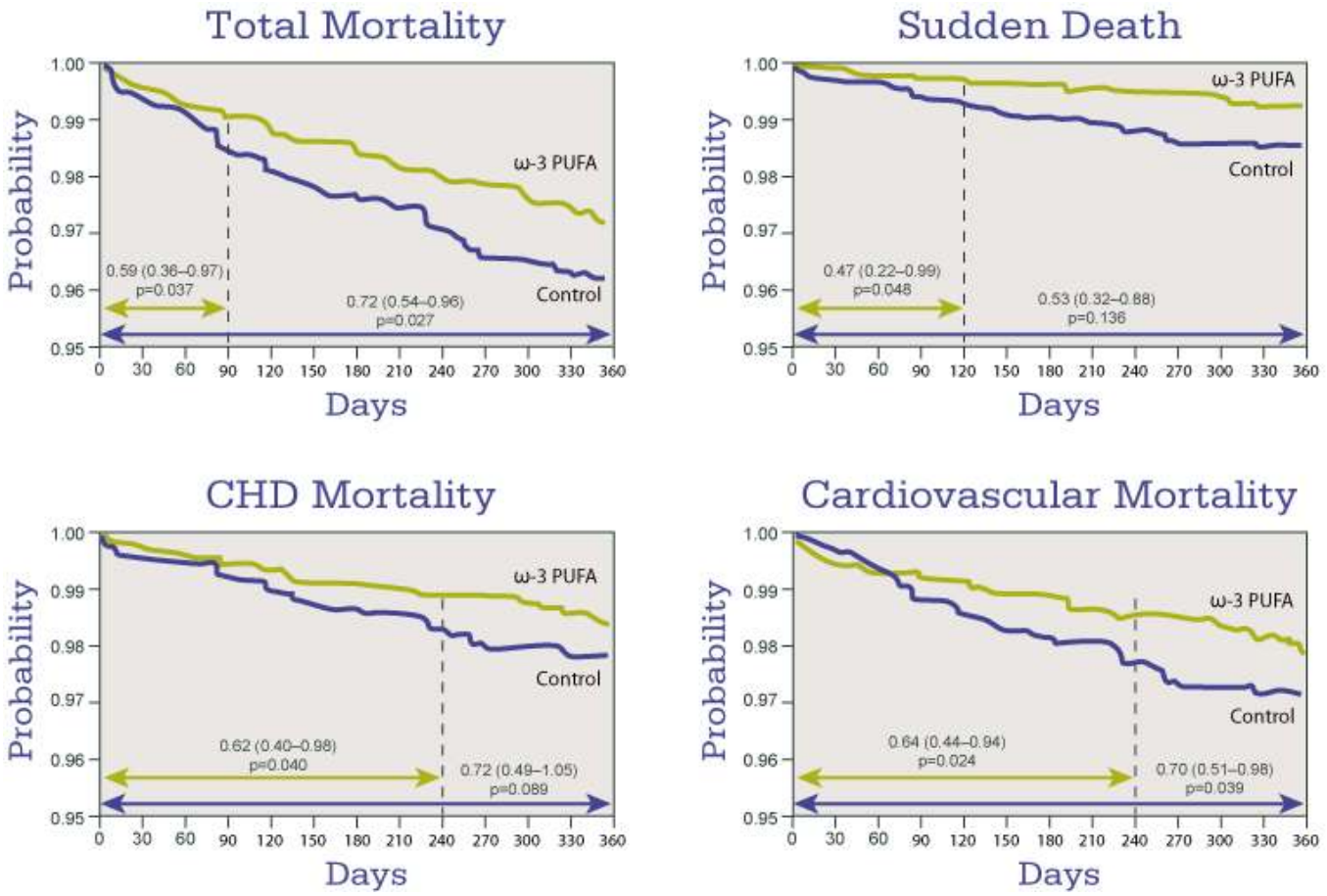
ORIGIN Study Questions

IFG, IGT, 또는 당뇨병 초기의 **고위험** 환자에 **insulin glargine**을 사용하여 정상 공복혈당을 목표로 하는 인슐린 대체 요법을 시행하면 표준 혈당 조절법 보다 심혈관 합병증의 위험을 감소시키는가?

IFG, IGT, 또는 당뇨병 초기의 고위험 환자에 **Ω-3 PUFA** 보충제는 심혈관 합병증의 위험을 감소시키는가?

GISS-Prevenzione study: Fish oil and post-MI prognosis

11,323 patients, with recent MI (median 16 days post-MI) over 3.5 years

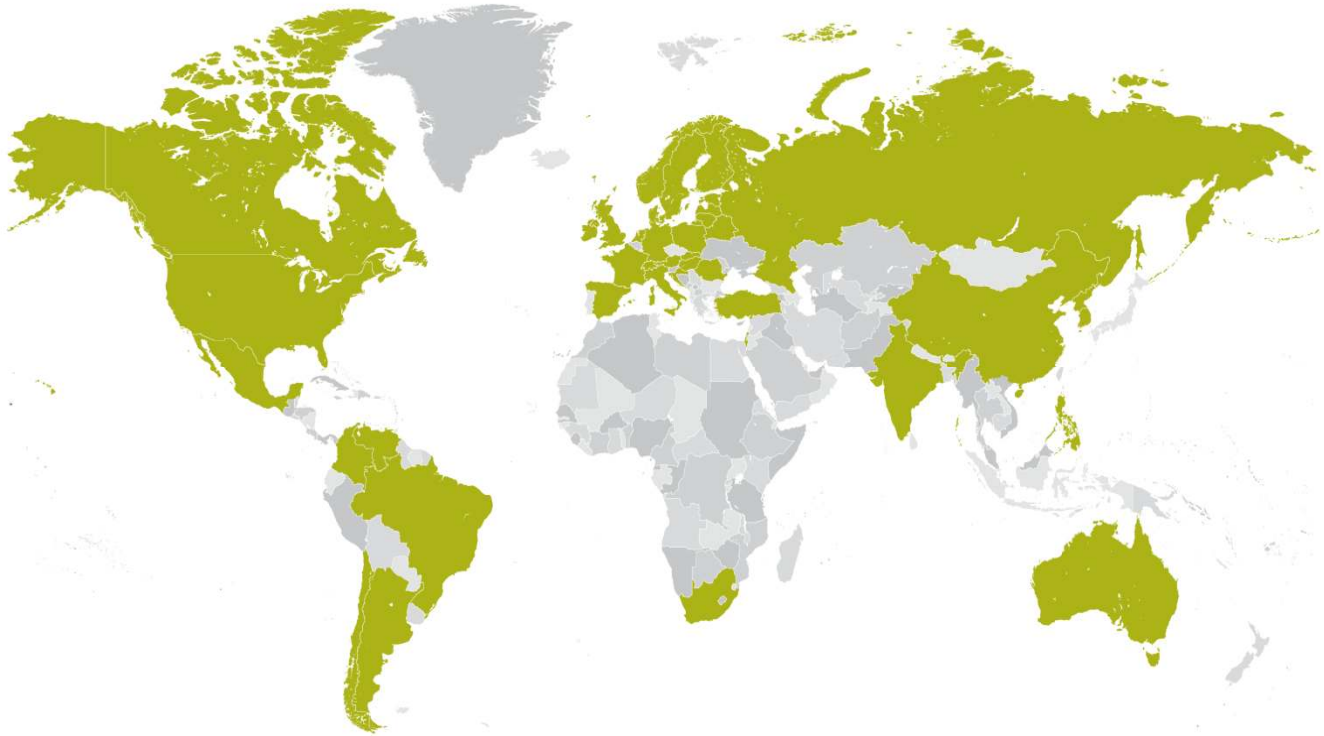


CHD, coronary heart disease. EPA, eicosapentaenoic acid.
MI, myocardial infarction. PUFA, polyunsaturated fatty acid.

Marchioli R, et al. *Circulation* 2002;105:1897-903.

ORIGIN: An international trial

- Led by an independent steering committee
- 40 countries, >12500 patients, 6.3 years of follow-up



Gerstein HC, et al. *Am Heart J* 2008;155:26-32.

ORIGIN: An international trial

Metrics Global vs. Korea	Site		Number of Pt	
	Initation	Active	Screen	Random
Global	538	578	15374	12612
Korea	8	8	131	131

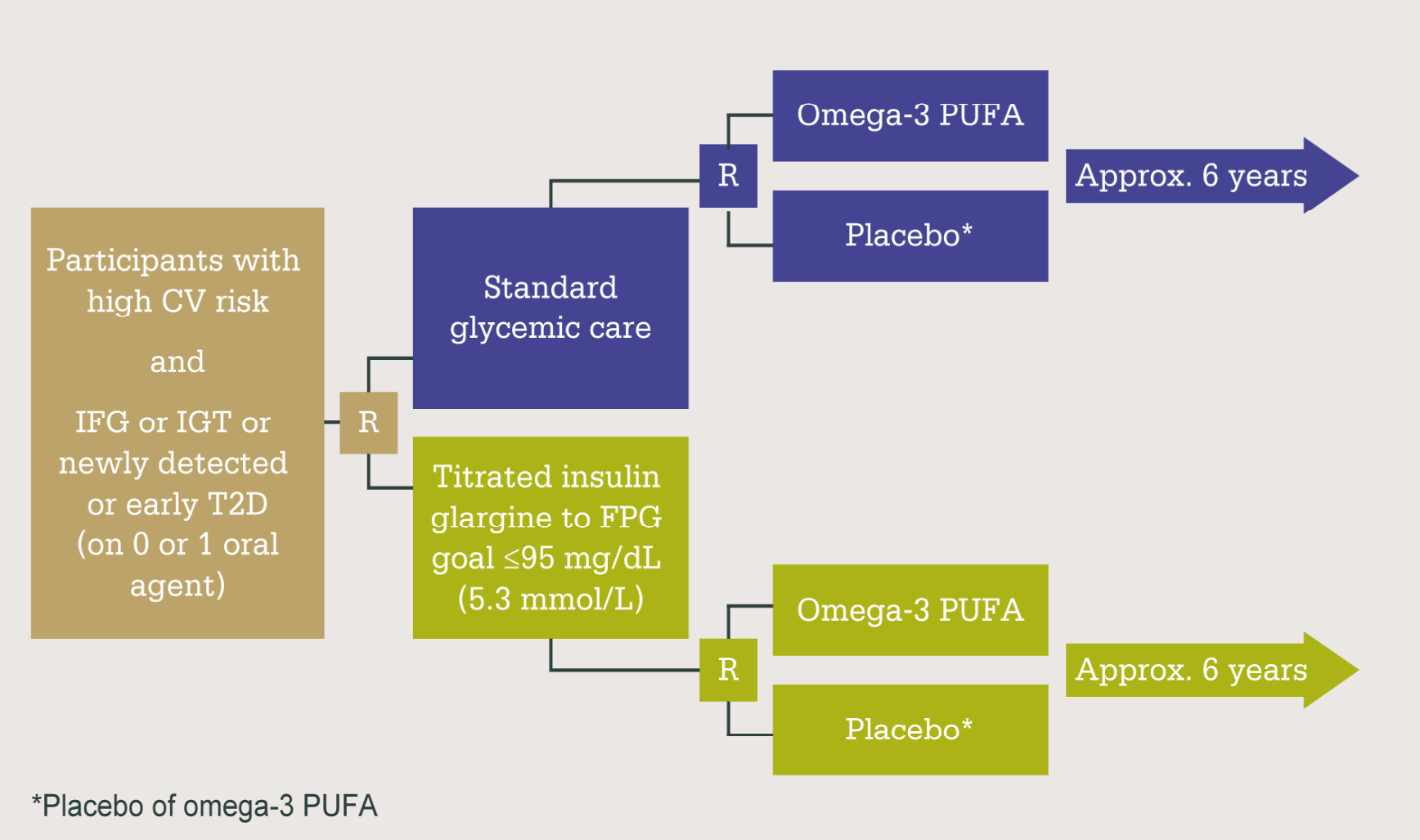
Gerstein HC, *et al*. *Am Heart J* 2008;155:26–32.

Inclusion criteria

- Men and women aged ≥50 years
- At high risk for CV event
- a) IFG, IGT, or newly detected diabetes
- b) established type 2 diabetes on stable therpay with 0 or 1 oral agent

Gerstein HC, *et al*. *Am Heart J* 2008;155:26–32.

ORIGIN: Assessing the effect of insulin glargine on cardiovascular complications in early T2DM



Gerstein HC, *et al*. *Am Heart J* 2008;155:26–32.

The ORIGIN Trial: Outcome measures

- Primary outcomes
  - Incident CV death, non-fatal MI, elevated cardiac markers and/or new electrocardiographic changes, or non-fatal stroke
  - These events plus a revascularization procedure or hospitalization for heart failure
- Secondary outcomes
  - Each component of the primary outcomes
  - All-cause mortality
  - Microvascular events
  - New type 2 diabetes

Gerstein HC, et al. *Am Heart J* 2008;155:26-32.

What can we expect to learn from ORIGIN?

- Advancing scientific knowledge about insulin glargine related to:
  - Cardiovascular events
  - Progression to diabetes from IFG/IGT
  - Microvascular complications
  - Beta cell function, carotid atherosclerosis, cardiac function, autonomic function, cognitive function, bone density (substudies)
  - Hypoglycemia
  - All-cause mortality
  - Cancer incidence
- Epidemiology of early Type 2 diabetes worldwide

Gerstein HC, et al. *Am Heart J* 2008;155:26-32.

ORIGIN: Baseline Characteristics

Category	(mean±SD or %)
N	12,612
Age	64±8
Gender F/M	35/65
BMI	29.8±5.2
Previous CVD (%)	66
Previous albuminuria (%)	15
Previous diabetes (%)	82
Newly detected diabetes (%)	6
IFG and/or IGT (%)	12
Known duration, years	5±6
Anti-hyperglycemic treatment	0-1 OAD
Metformin (%)	27
Insulin secretagogue (%)	31
Diabetes diagnosed entry (%)	6
A1c (%)	6.5±1.0
FPG (mg/dL)	132±3.6

ORIGIN: Comparison with other CV outcome trials

	ACCORD[1]	VADT[2]	ADVANCE[3]	ORIGIN[4]
n	10,251	1,792	11,140	12,612
Age yrs	62	60	66	64
Diabetes yrs	10	11.5	8	5.4
Not known to have DM (%)	0	0	0	18
Macrovasc. comp. (%)	35	40	32	66
Baseline A_{1c} %	8.3	9.4	7.5	6.5
Intensive Rx target	A_{1c} < 6%	A_{1c} < 6%	A_{1c} ≤ 6.5 %	FPG ≤5.3 mmol/L
Intervention	Multiple drugs	Multiple drugs	Gliclazide ± others	Glargine ± others

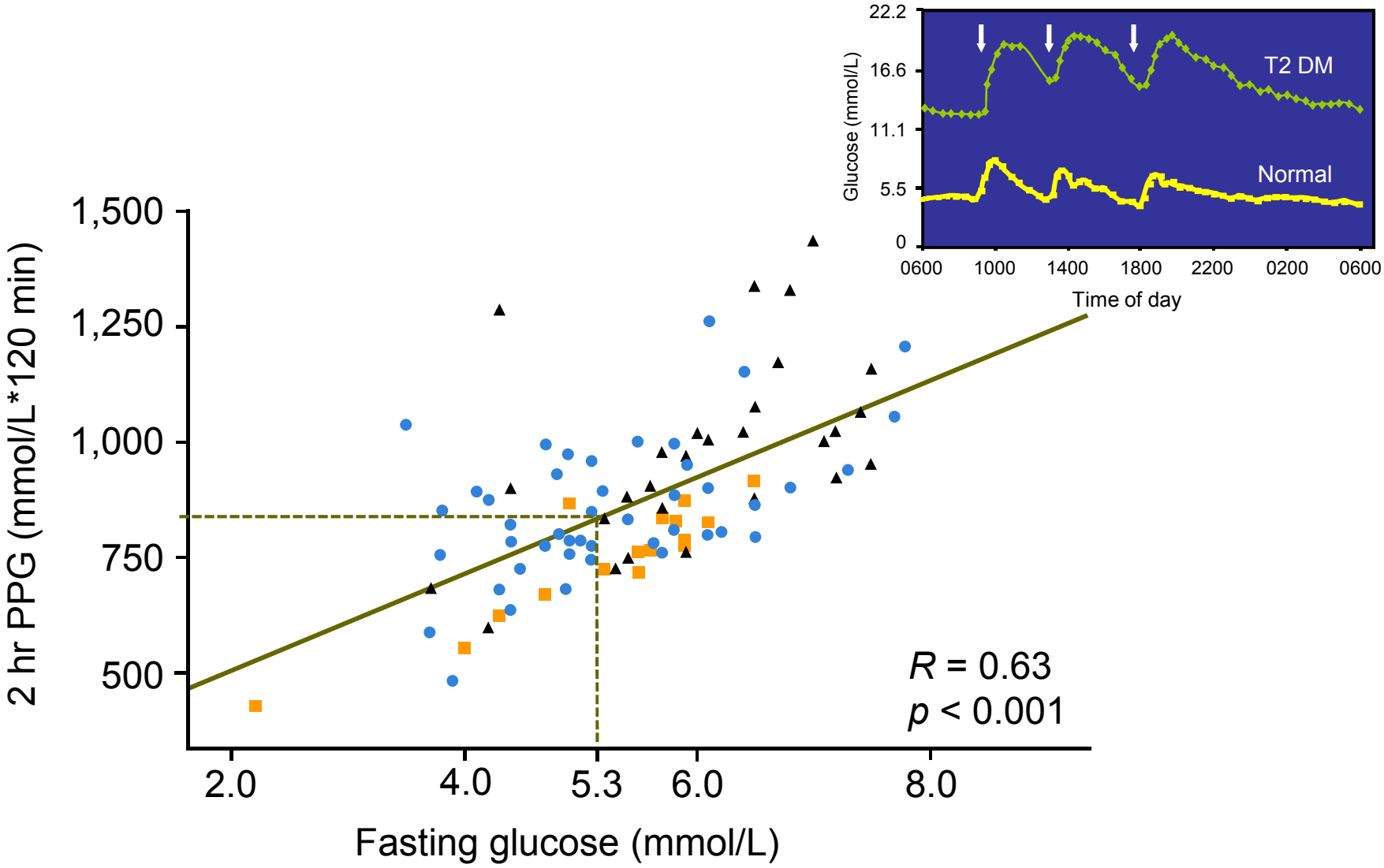
Early diabetes; high CV risk

1. The ACCORD Study Group. *N Engl J Med* 2008;358:2545-59.
2. Duckworth W, et al. *N Engl J Med* 2009;360:129-39.
3. The ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–72.
4. Gerstein HC, et al. *Am Heart J* 2008;155:26-32.

ORIGIN *vs.* UKPDS

	ORIGIN (N=12612)	UKPDS (N=3867)
Population Glycaemic Profile	IFG, IGT (12%) Newly diagnosed T2D (6%) Previously diagnosed T2D (82%)	Newly diagnosed T2D (100%)
Population CV Risk Profile	66% CV event Secondary prevention Age >50	No CV event Primary prevention Age 25-65
Glycemic target	FBG <5.3mmol/L	FBG <6mmol/L
Study Intervention	Normoglycemia with insulin therapy vs Standard glycemic care Insulin therapy is insulin glargine Insulin can be used in the control arm as a rescue medication only and insulin glargine can not be used.	SU/Insulin therapy targeting FBG <6mmol/L vs with conventional therapy targeting FPG <15mmol/L Insulin is Ultratard (not a basal analogue)
Baseline A1C	6.5%	8.1%
Started in	2003	1987

Tight control of FPG reduces PPG: ORIGIN-sub study



Hanefeld M, *et al*. *Diabet Med* 2010; 27:175–80;
Polonsky et al, *N Engl J Med* 1988.

Outcome Reduction with Initial Glargine Intervention

결과는 **2012**년
ADA에서 발표될 예정

Conclusions (1)

- **Dysglycemia** is an independent risk factor for cardiovascular disease in the general population, regardless of diabetes status
- **Intensive glycemic control** in people with newly diagnosed diabetes reduces their long-term risk of cardiovascular disease
- **Several ongoing trials** are assessing the effects that different agents or strategies used for lowering levels of glucose have on cardiovascular outcomes

Conclusions (2)

- Treatment with insulin glargine provides effective glycemic control with better results achieved with earlier use
  - Data on the effects of glargine on CV complications in early T2DM are awaited (ORIGIN study)
- Despite the evidence for the beneficial effects of early insulin initiation, treatment is often delayed