Update on Diabetes - 2010

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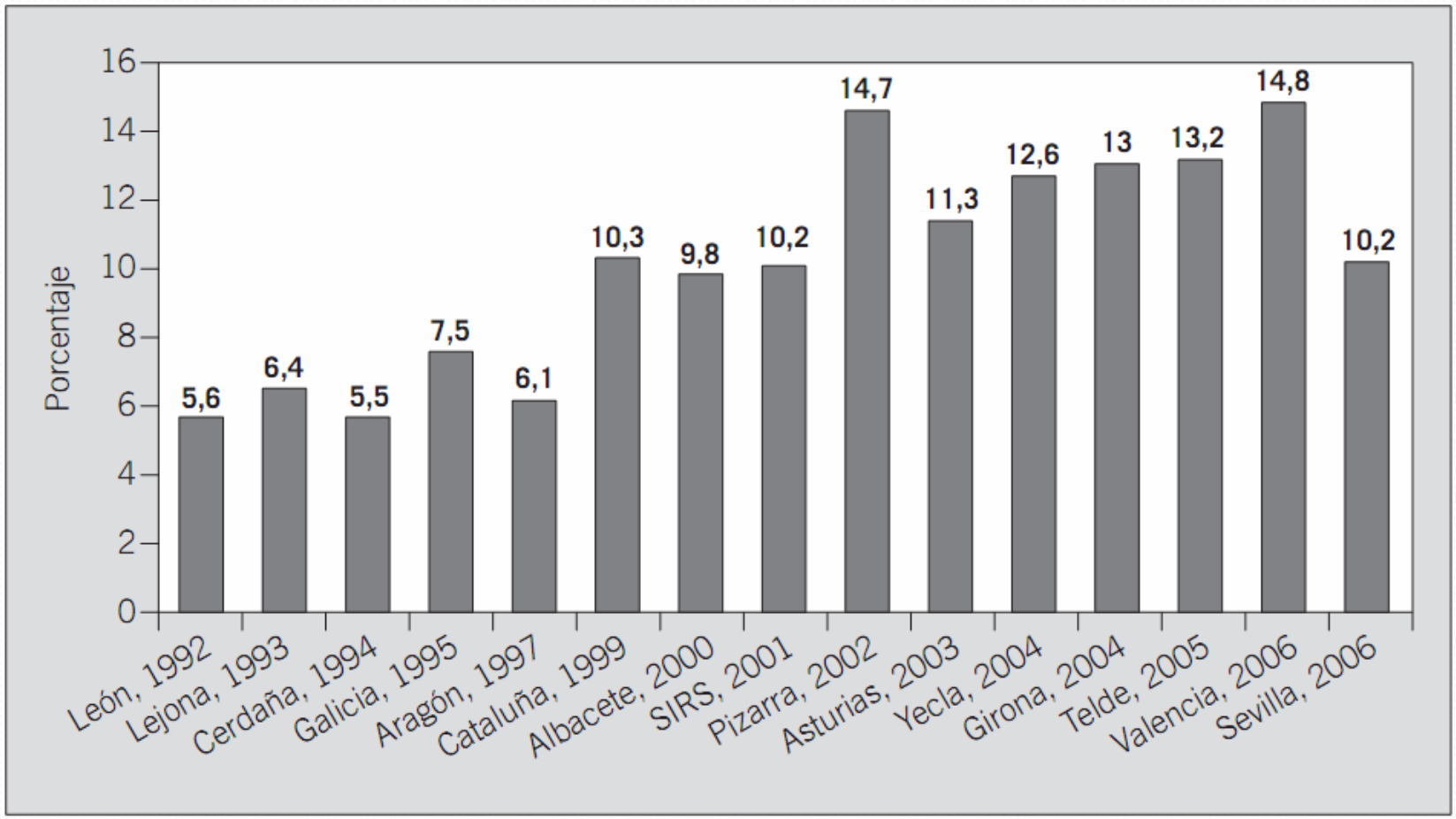
Multiplicities of interest

- My patients with diabetes
- Consultant/advisor: BMS/Astra Zeneca, Merck, Novartis, Dainippon Sumitomo Pharma America, Forest Laboratories, Boehringer Ingelheim, Biodel, Medtronics
- Speaker: Merck, NovoNordisk, GSK, Boehringer Ingelheim , Medtronics
- Stockholder: Baxter International, CVS Caremark, Roche Holdings, St Jude Medical, Novartis

Update on Diabetes - 2010

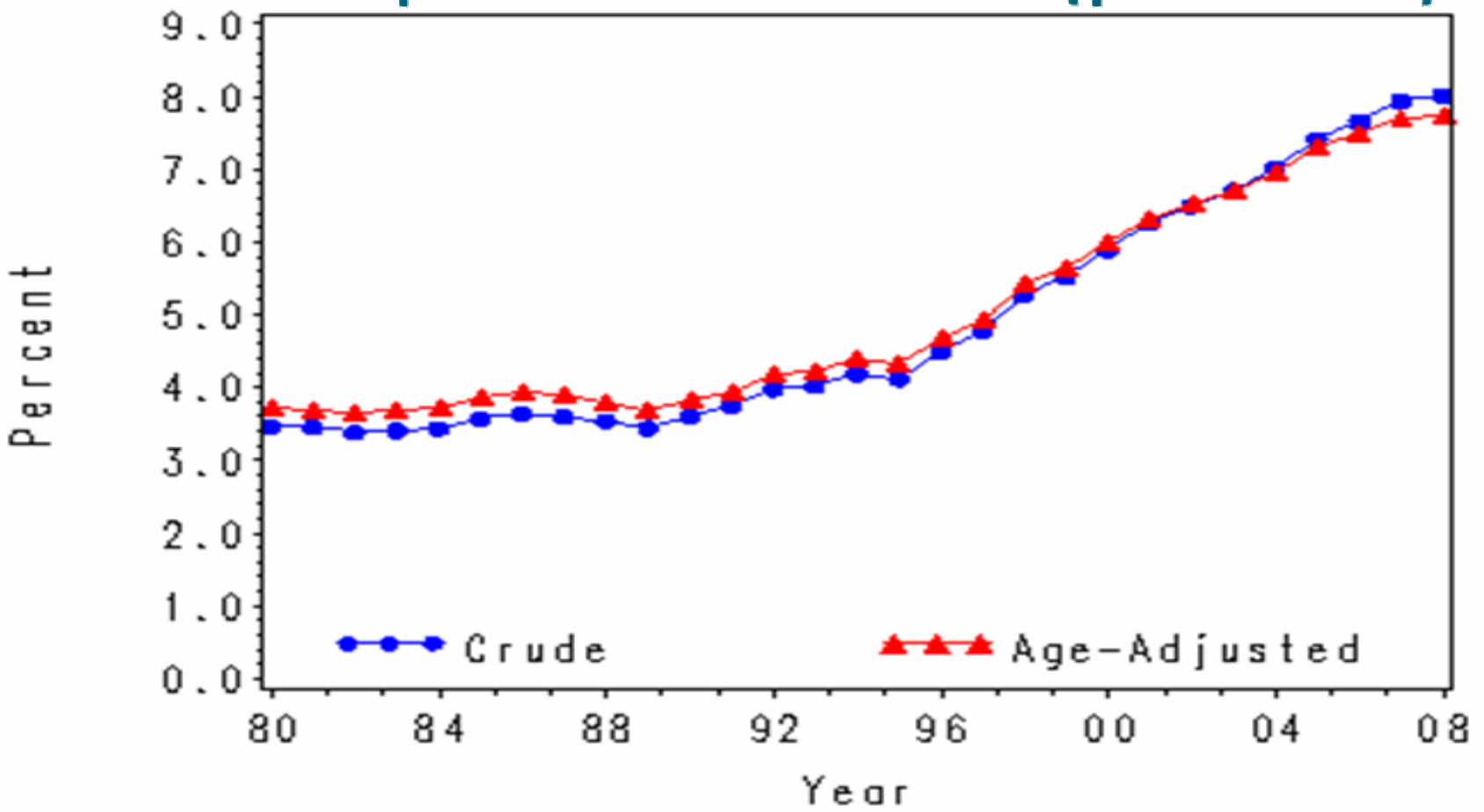
- Diabetes epidemiology
- ACCORD glycemia: further understanding of outcome
  - Hypoglycemia effect
  - Different A1c-outcome relationship of standard vs. intensive arms
  - Microvascular effects
- ACCORD lipids and blood pressure
- Understanding A1c use for diagnosis and for treatment
- Type 1 diabetes treatment: The STAR-3 trial

Diabetes prevalence: Spain



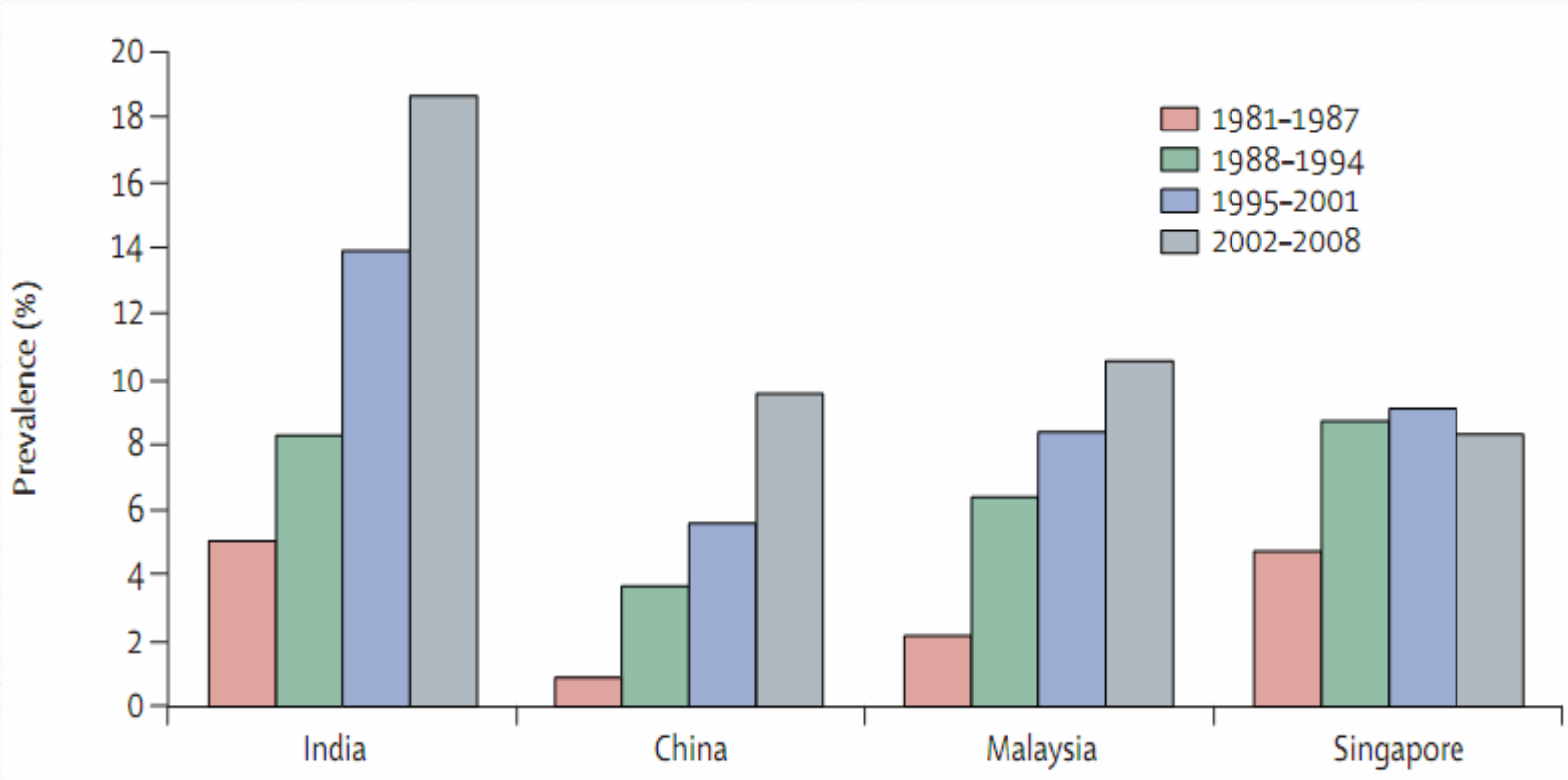
Valdés et al Med Clin (Barc) 2007 129 352

Diabetes prevalence: US (percent)



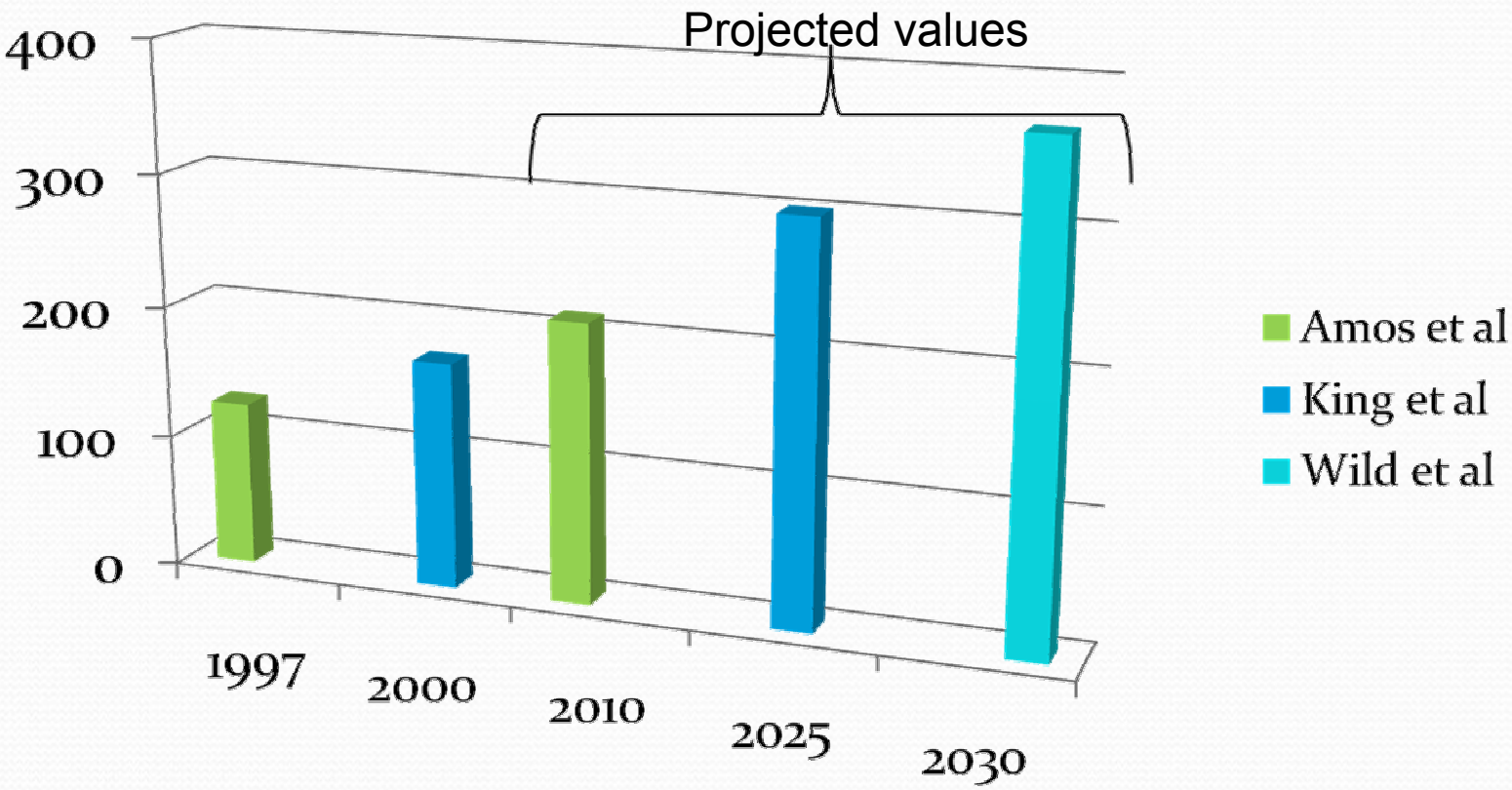
National Diabetes Surveillance System. Available at: http://www.cdc.gov/diabetes

Diabetes prevalence: Asia (percent)



Ramachandran et al. Lancet 2010; 375: 408–18

Diabetes prevalence: world(/10^6)



Meetoo et al. British Journal of Nursing 2007;16:1002

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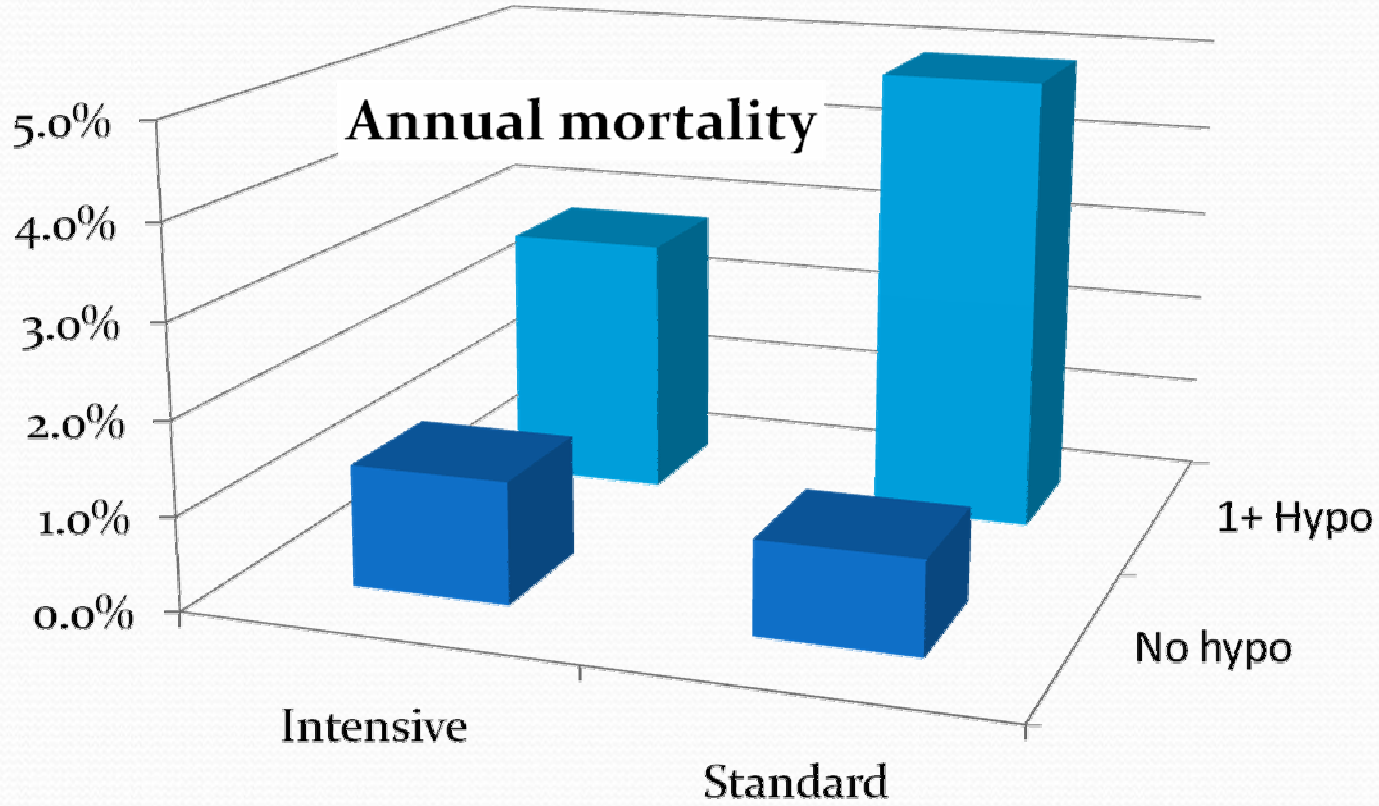
Action to Control Cardiovascular Risk in Diabetes (ACCORD): Severe Hypoglycemia

- Annual rates: intensive 3.3% vs. standard 1.1%.
- Interaction of hypoglycemia with treatment:
  - 9,546 persons without severe hypoglycemia
    - Mortality risk 24% ↑ in intensive treatment group
  - 705 persons with ≥1 severe hypoglycemia
    - Mortality ~3-fold greater than among those not experiencing hypoglycemia
    - Mortality risk 60% ↓ in intensive treatment group

Bloomgarden Z. *Diabetes Care*. 2008 Sep;31(9):1913-9.

ACCORD: severe hypoglycemia



Bonds et al. BMJ 2010;340:b4909

Hypoglycemia vs. mortality: metaregression analysis

	Mortality Odds Ratio	**Severe hypoglycemia, % ↑ in intervention groups**
Proactive, UKPDS, ADVANCE	↓ 0.08 to 0.24	0.2-0.8%
ACCORD, VADT	↑ 0.24 to 0.36	1.5-3.0%

Cardiovascular Diseases (2008) 10, 004

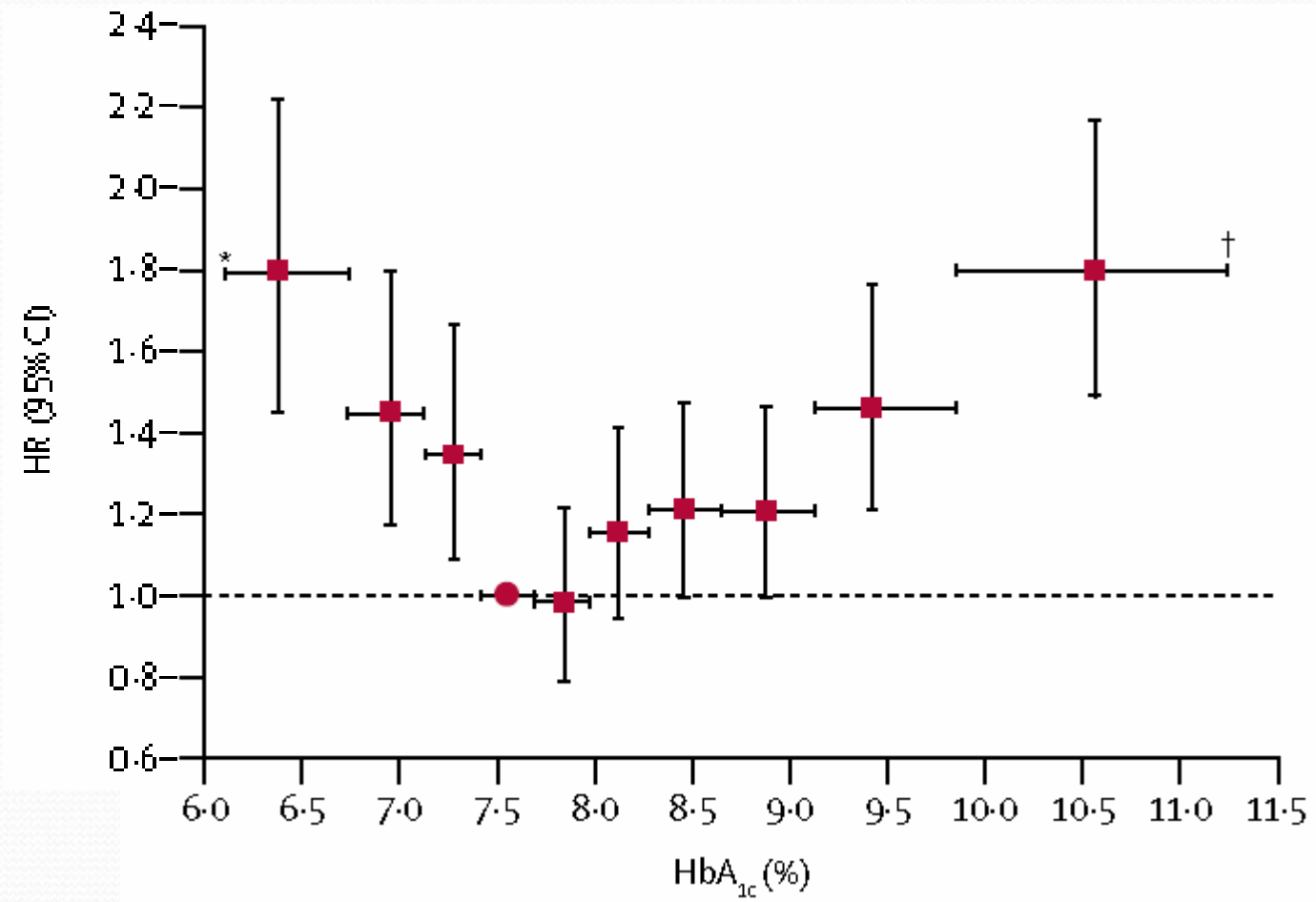
ACCORD: mortality

	Intensive	Standard
CVD death	135	94
Unexpected/sudden	86	67
Myocardial	19	13
CV procedure	10	3
Arrhythmia	4	10
Stroke	9	11
Other CVD	8	10

Two thirds were unexpected/sudden death

ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559.

Adverse effect of insulin intensification from oral monotherapy, mortality risk vs. A1c, n=20,005



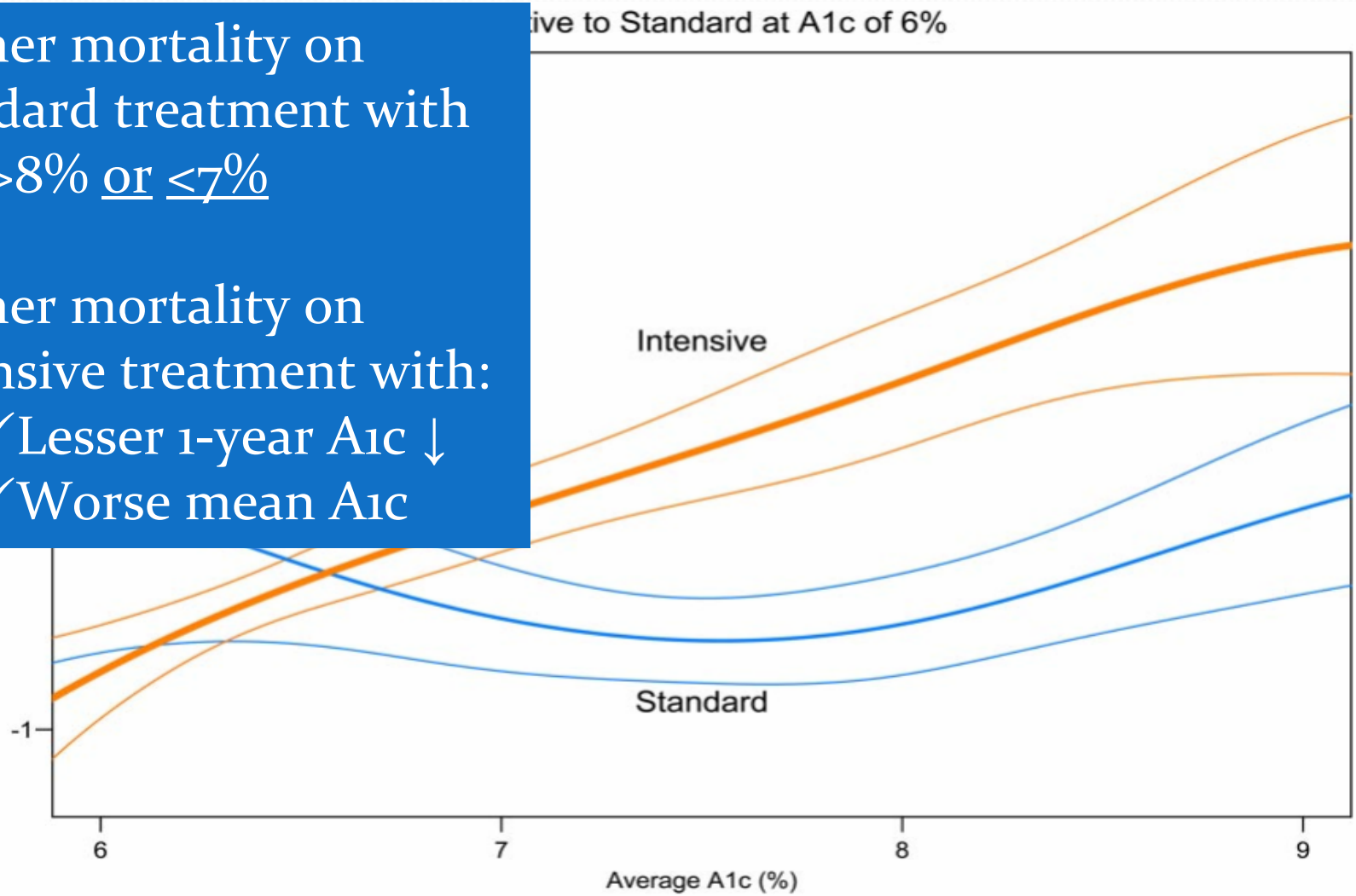
Currie et al. Lancet, 2010

ACCORD: mortality vs. on-trial A1c

Higher mortality on standard treatment with A1c >8% or ≤7%

Higher mortality on intensive treatment with:

- ✓Lesser 1-year A1c ↓
- ✓Worse mean A1c



Diabetes Care 2010 ;33:983-990

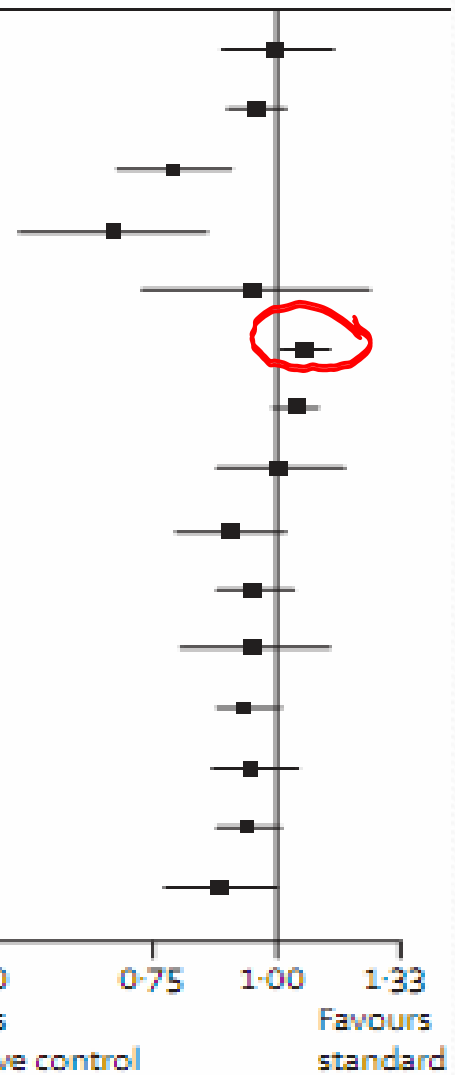
ACCORD microvascular outcomes

	At transition to standard therapy (February, 2008)*			End of study (June, 2009)		
	Intensive glycaemia control	Standard glycaemia control	p value	Intensive glycaemia control	Standard glycaemia control	p value
	Intensive glycaemia control		**Standard glycaemia control**		**p value**	
	n	Median (IQR)	n	Median (IQR)		
HbA_{1c} concentration (%)	4517	6·3% (5·9–7·0%)	4577	7·6% (7·0–8·2%)	<0·0001	
Fasting serum glucose	4232	5·88 (4·94–7·33)	4292	8·16 (6·66–9·93)	<0·0001	
Systolic blood pressure (mm Hg)	4524	127 (116–138)	4583	128 (116–139)	0·0144	
Diastolic blood pressure (mm Hg)	4524	67 (60–74)	4583	68 (61–75)	0·0003	
HDL cholesterol in women	1634	1·22 (1·04–1·45)	1633	1·19 (1·01–1·40)	0·0050	
HDL cholesterol in men	2610	1·01 (0·85–1·22)	2682	0·98 (0·83–1·17)	0·0014	
Triglycerides	4245	1·43 (1·01–2·10)	4316	1·59 (1·11–2·36)	<0·0001	
Body-mass index (kg/m²)	3768	33 (29–37)	3789	32 (28–36)	<0·0001	
Serum creatinine (μmol/L)	4395	87·5 (73·4–107·0)	4466	87·5 (72·5–107·0)	0·9612	
Urine albumin:creatinine ratio (mg/mmol)	4297	1·19 (0·64–3·42)	4380	1·36 (0·7–4·47)	<0·0001	

Accord microvascular. Lancet 2010;376:419

Glycemic groups: to transition

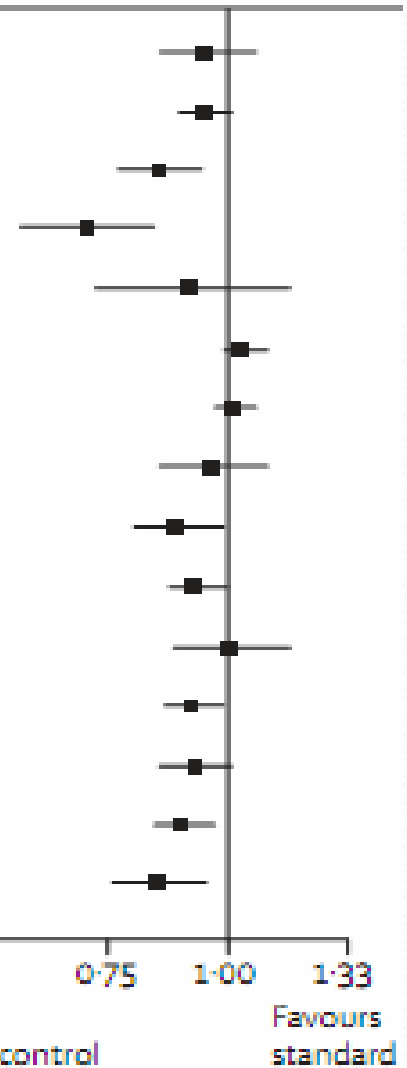
	Intensive		Standard	
	Events/n	%	Events/n	%
First composite	443/5107	8·7	444/5108	8·7
Second composite	1591/5107	31·2	1659/5108	32·5
Neph-1: incident microalbuminuria	399/3204	12·5	494/3232	15·3
Neph-2: incident macroalbuminuria	138/4334	3·2	199/4361	4·6
Neph-3: ESRD	911/5085	2·1	112/5108	2·2
Neph-4: doubling of SCr or >20 U eGFR decrease	2701/5035	53·6	2627/5034	52·2
Neph-5: any of Neph-2, Neph-3, or Neph-4	2788/5107	54·6	2760/5108	54·0
Eye-1: photocoagulation or vitrectomy	350/4886	7·2	347/4910	7·1
Eye-2: cataract surgery	447/4886	9·1	495/4910	10·1
Eye-3: three-line worsened visual acuity	911/5085	17·9	951/5085	18·7
Eye-4: severe loss of vision*	258/4651	5·5	273/4689	5·8
Neuro-1: neuropathy (MNSI score >2·0)	1277/2815	45·4	1338/2791	47·9
Neuro-2: loss of vibratory sensation	766/4209	18·2	805/4209	19·1
Neuro-3: loss of ankle jerk	1225/3298	37·1	1270/3265	38·9
Neuro-4: loss of sensation to light touch	424/4577	9·3	481/4564	10·5



Accord microvascular. Lancet 2010;376:419

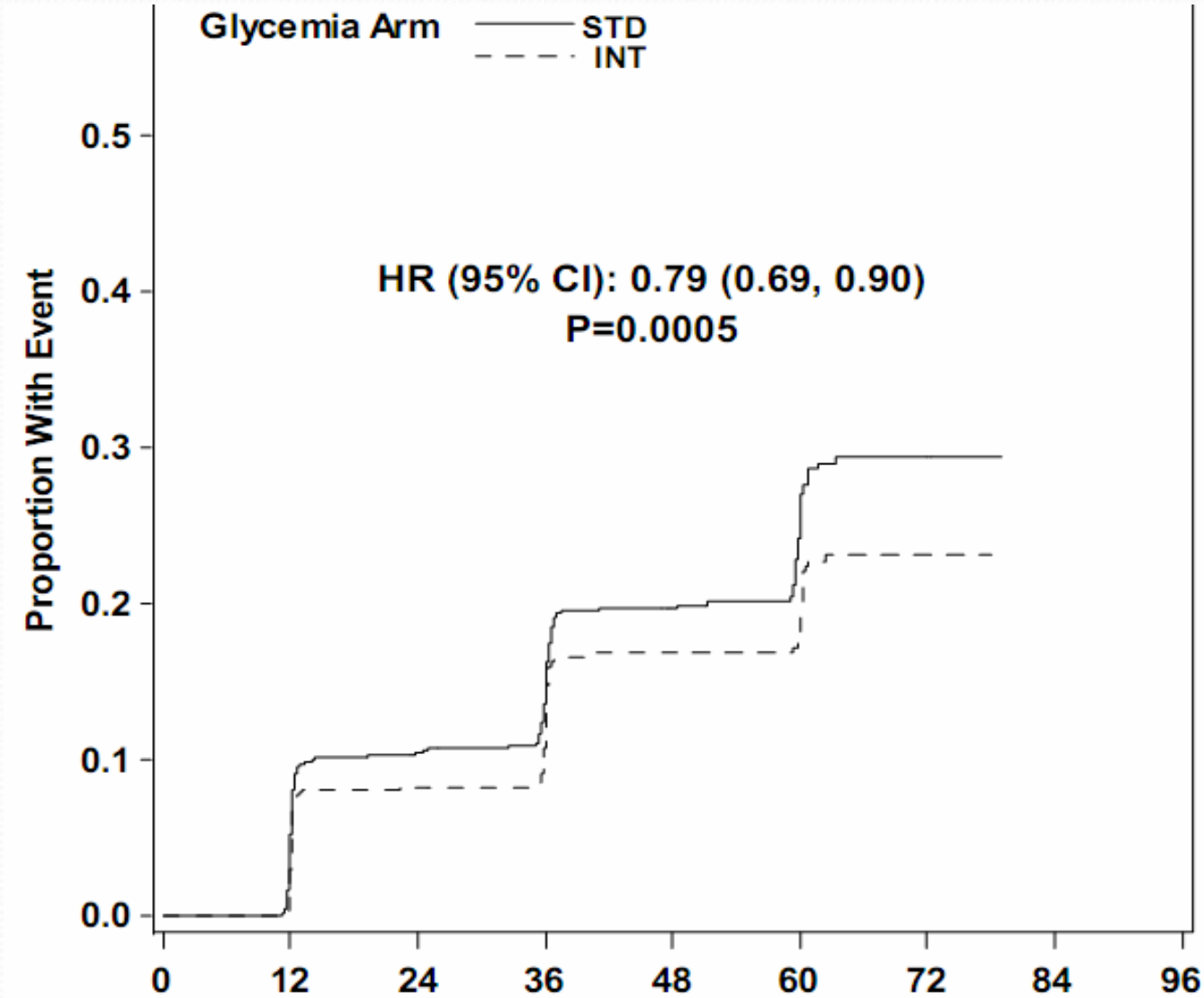
Glycemic groups: to study end

	Intensive		Standard	
	Events/n	%	Events/n	%
First composite	556/5119	10·9	586/5115	11·5
Second composite	1956/5119	38·2	2046/5115	40·0
Neph-1: incident microalbuminuria	720/3250	22·2	828/3273	25·3
Neph-2: incident macroalbuminuria	264/4397	6·0	362/4424	8·2
Neph-3: ESRD	138/5119	2·7	151/5115	3·0
Neph-4: doubling of SCr or >20 U eGFR decrease	2956/5041	58·6	2943/5035	58·5
Neph-5: any of Neph-2, Neph-3, or Neph-4	3077/5119	60·1	3107/5115	60·7
Eye-1: photocoagulation or vitrectomy	440/4915	9·0	456/4933	9·2
Eye-2: cataract surgery	696/4915	14·2	775/4933	15·7
Eye-3: three-line worsened visual acuity	1417/5089	27·8	1510/5088	29·7
Eye-4: severe loss of vision*	384/4748	8·1	385/4774	8·1
Neuro-1: neuropathy (MNSI score >2·0)	1573/2829	55·6	1640/2797	58·6
Neuro-2: loss of vibratory sensation	981/4227	23·2	1050/4217	24·9
Neuro-3: loss of ankle jerk	1514/3312	45·7	1612/3271	49·3
Neuro-4: loss of sensation to light touch	554/4596	12·1	645/4573	14·1



Accord microvascular. Lancet 2010;376:419

Microalbuminuria vs. glycemia



Accord microvascular. Lancet 2010;376:419

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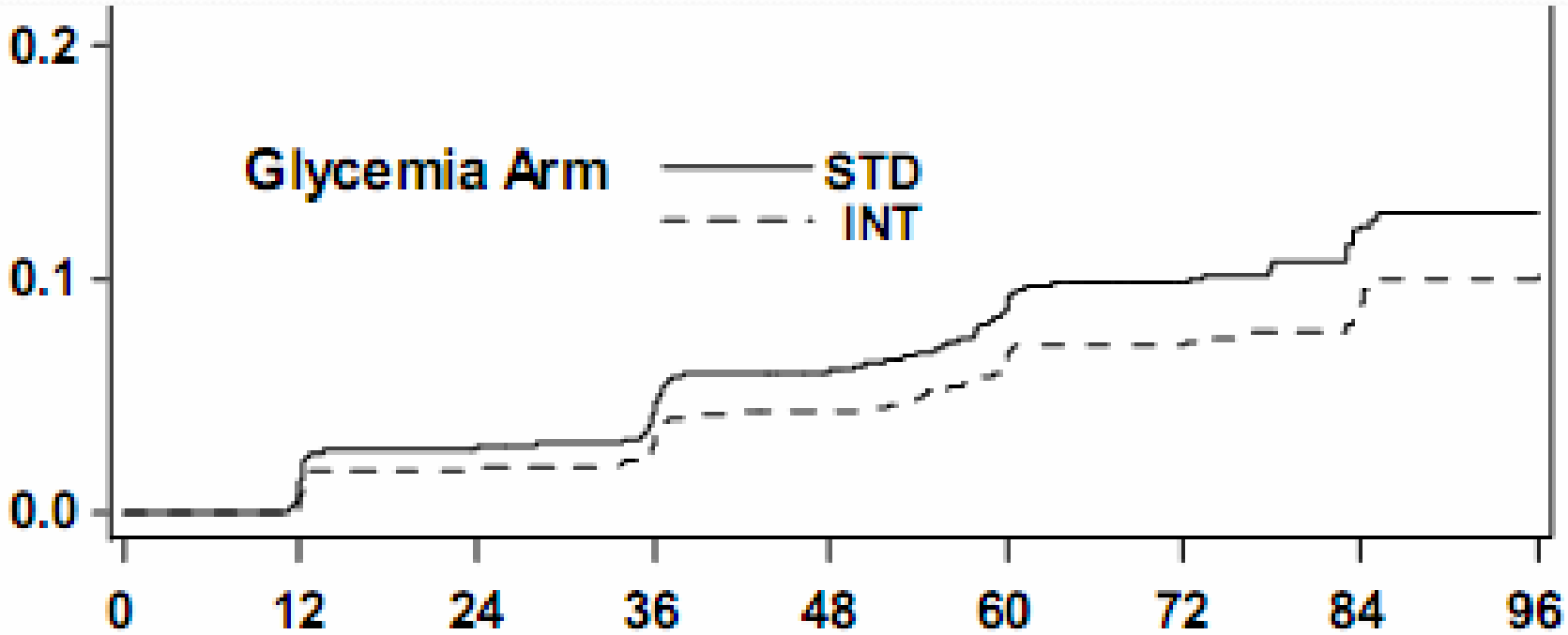
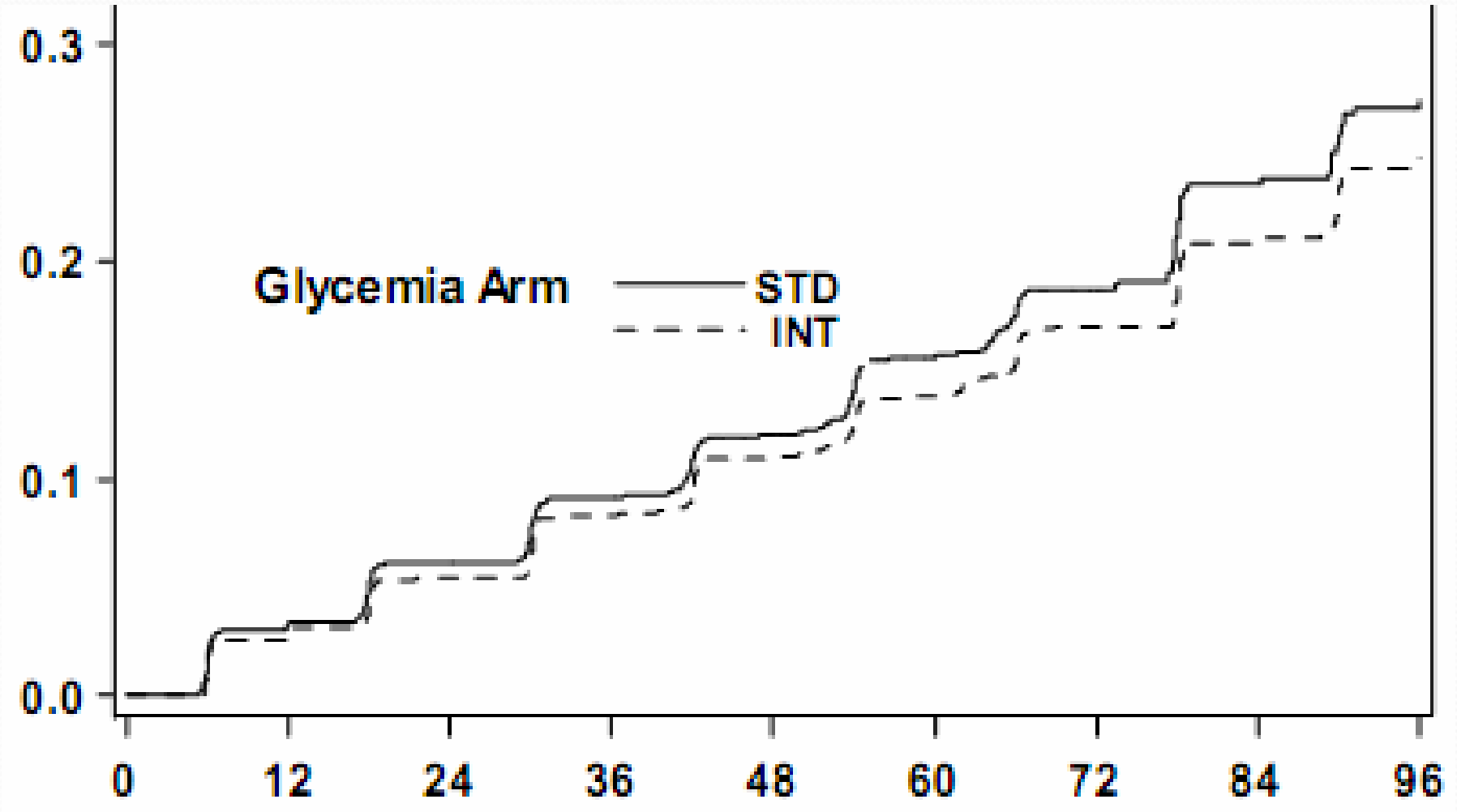


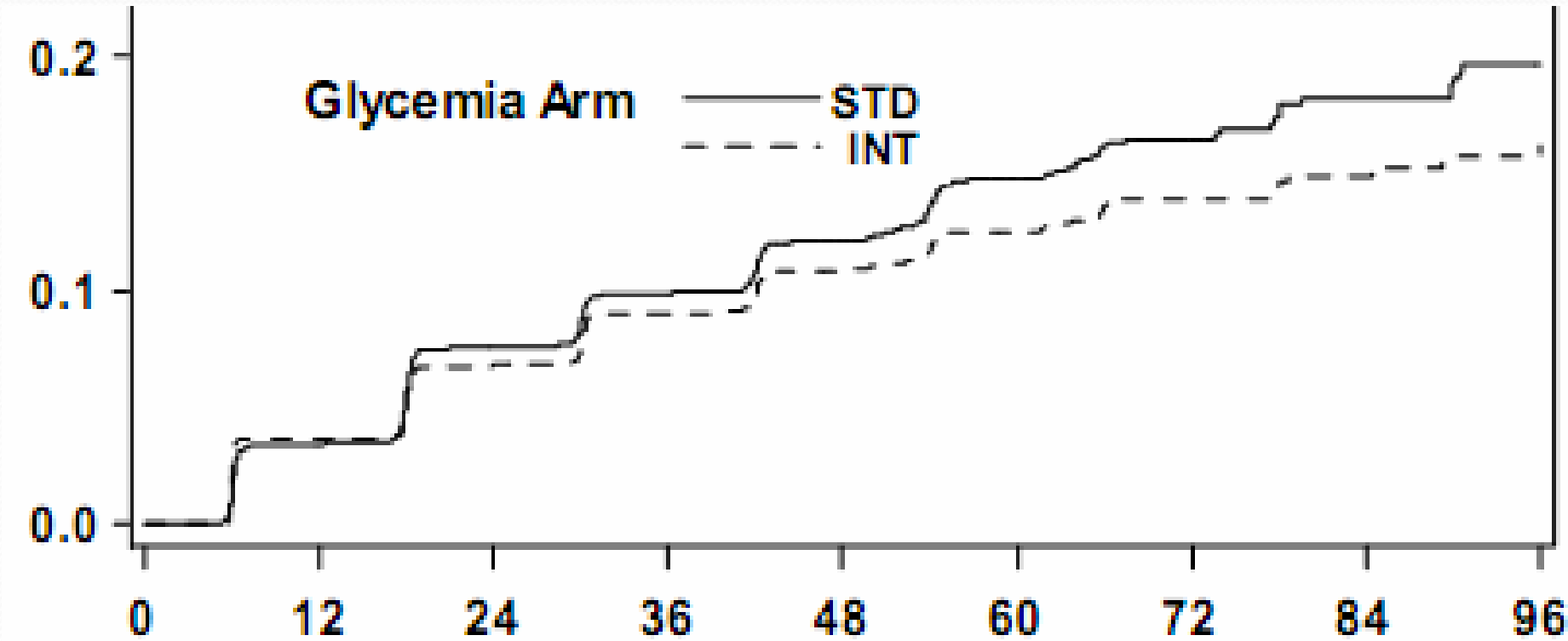
Accord microvascular. Lancet 2010;376:419

Cataract surgery vs. glycemia



Accord microvascular. Lancet 2010;376:419

Loss of light touch vs. glycemia



Accord microvascular. Lancet 2010;376:419

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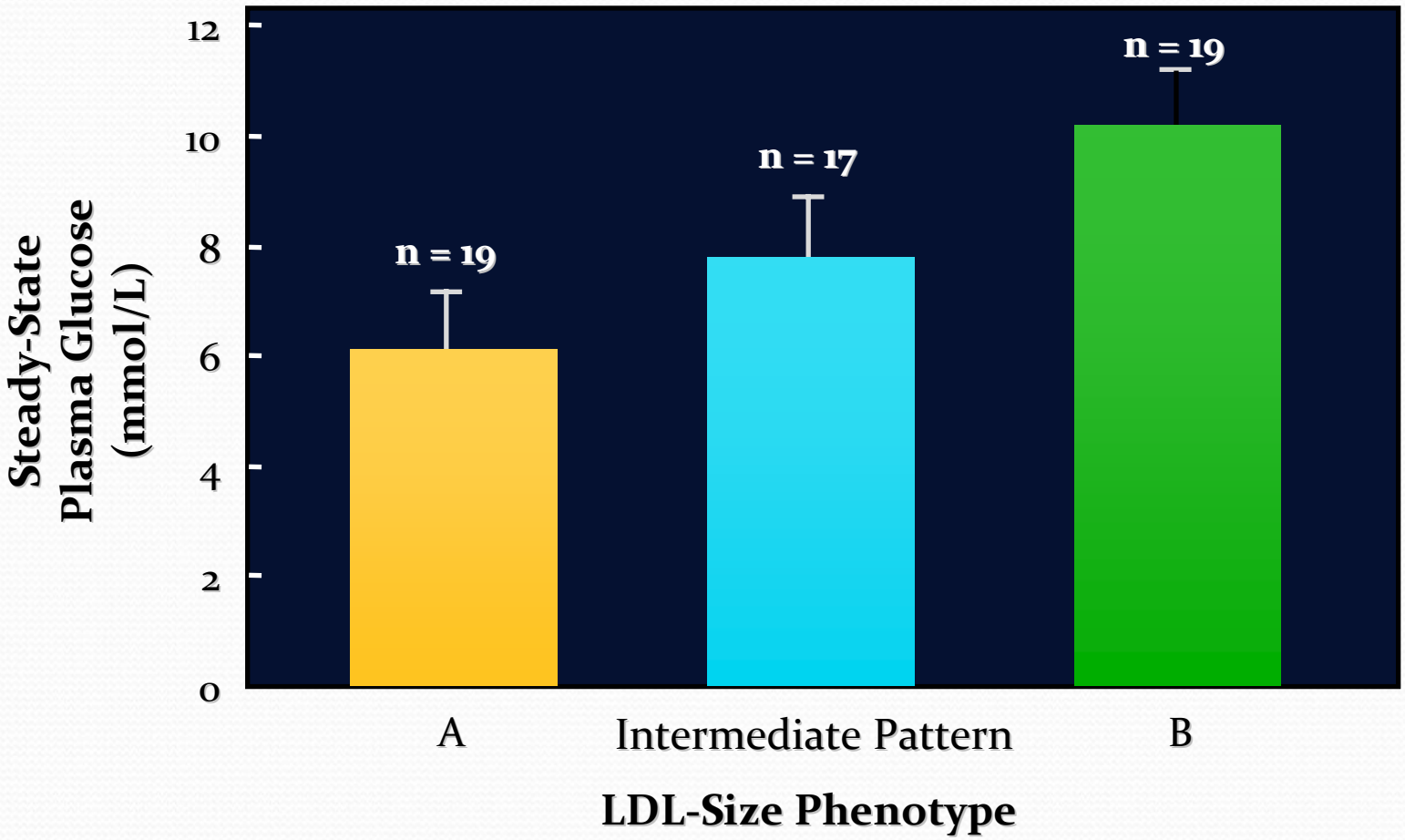
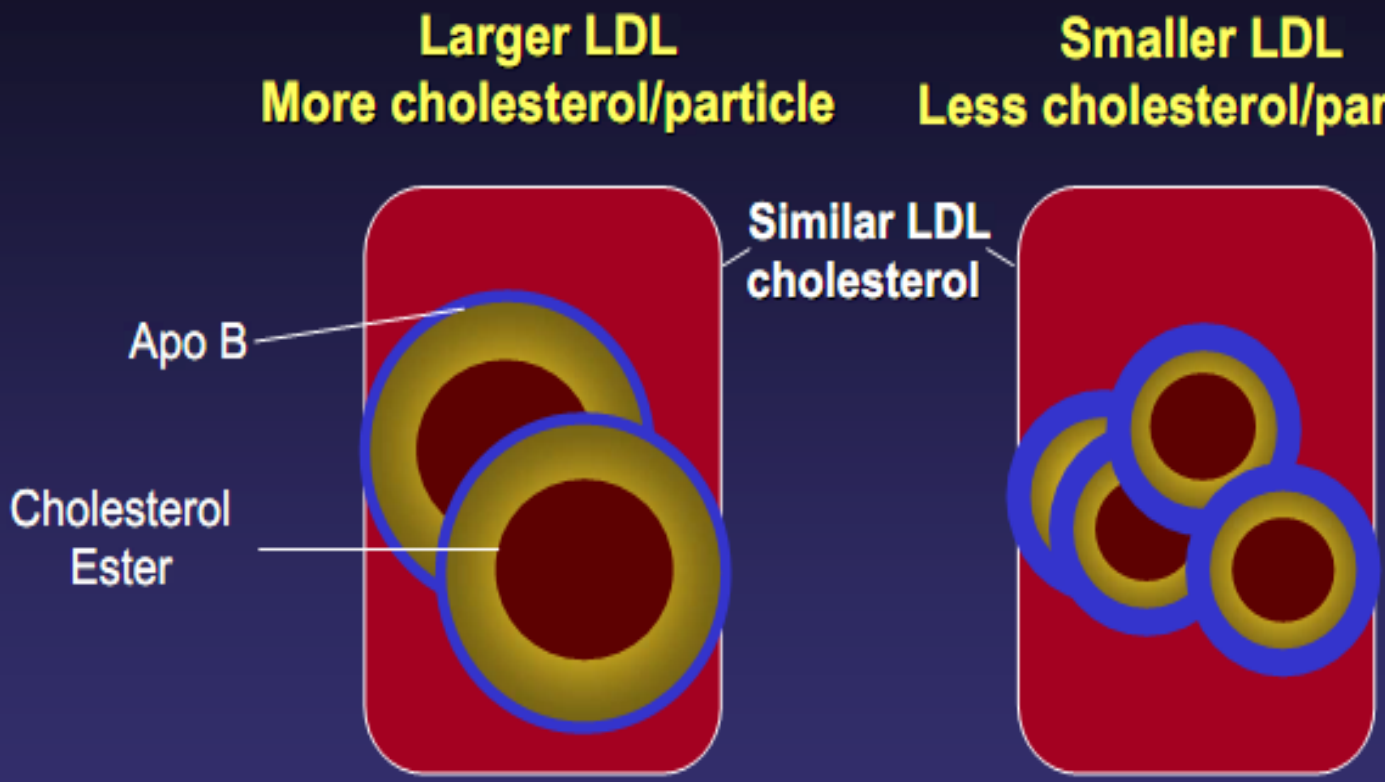
Association Between Small, Dense LDL and Insulin Resistance



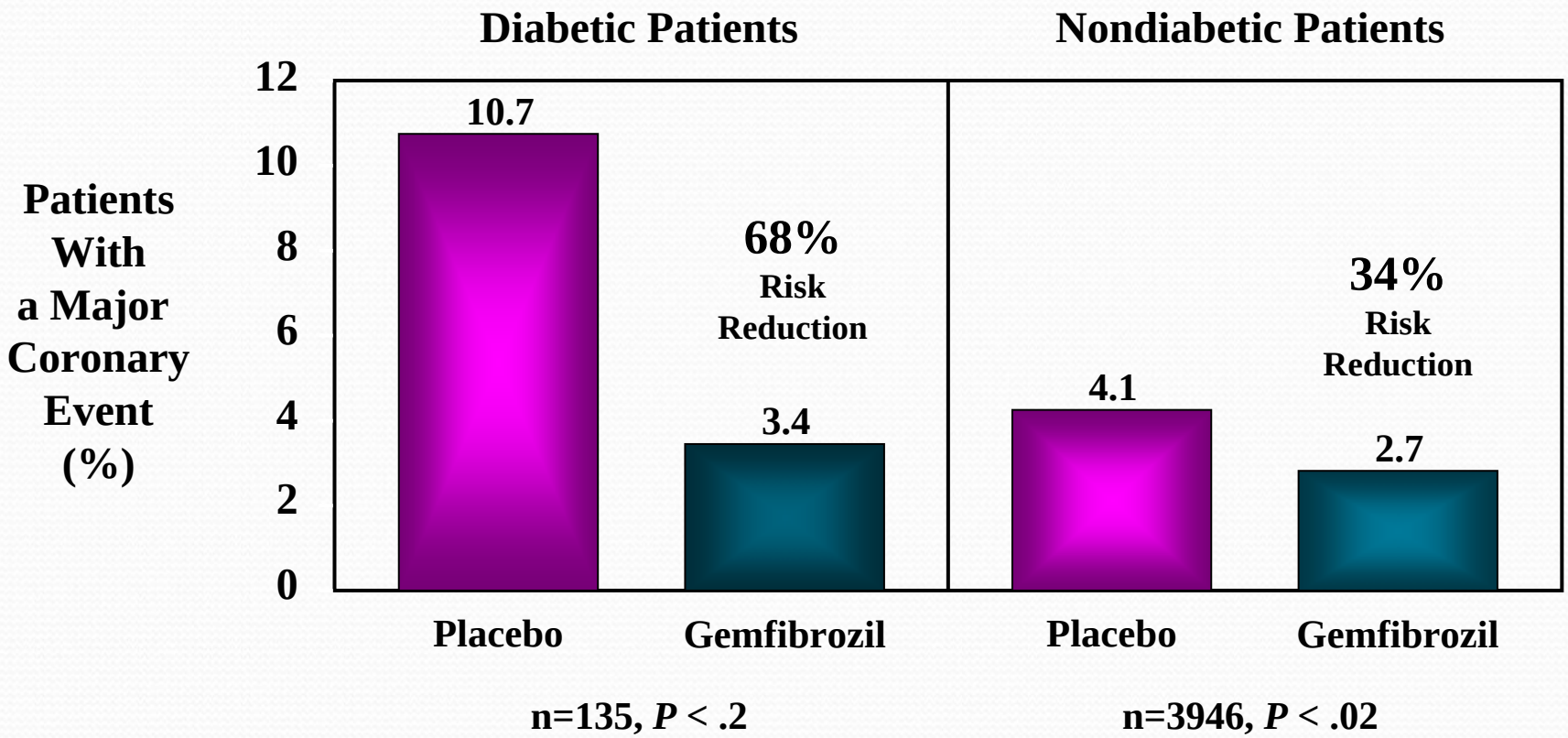
Reaven GM et al. J Clin Invest. 1993;92:141–146.

LDL-Cholesterol underestimates the number of LDL particles when levels of small LDL are increased



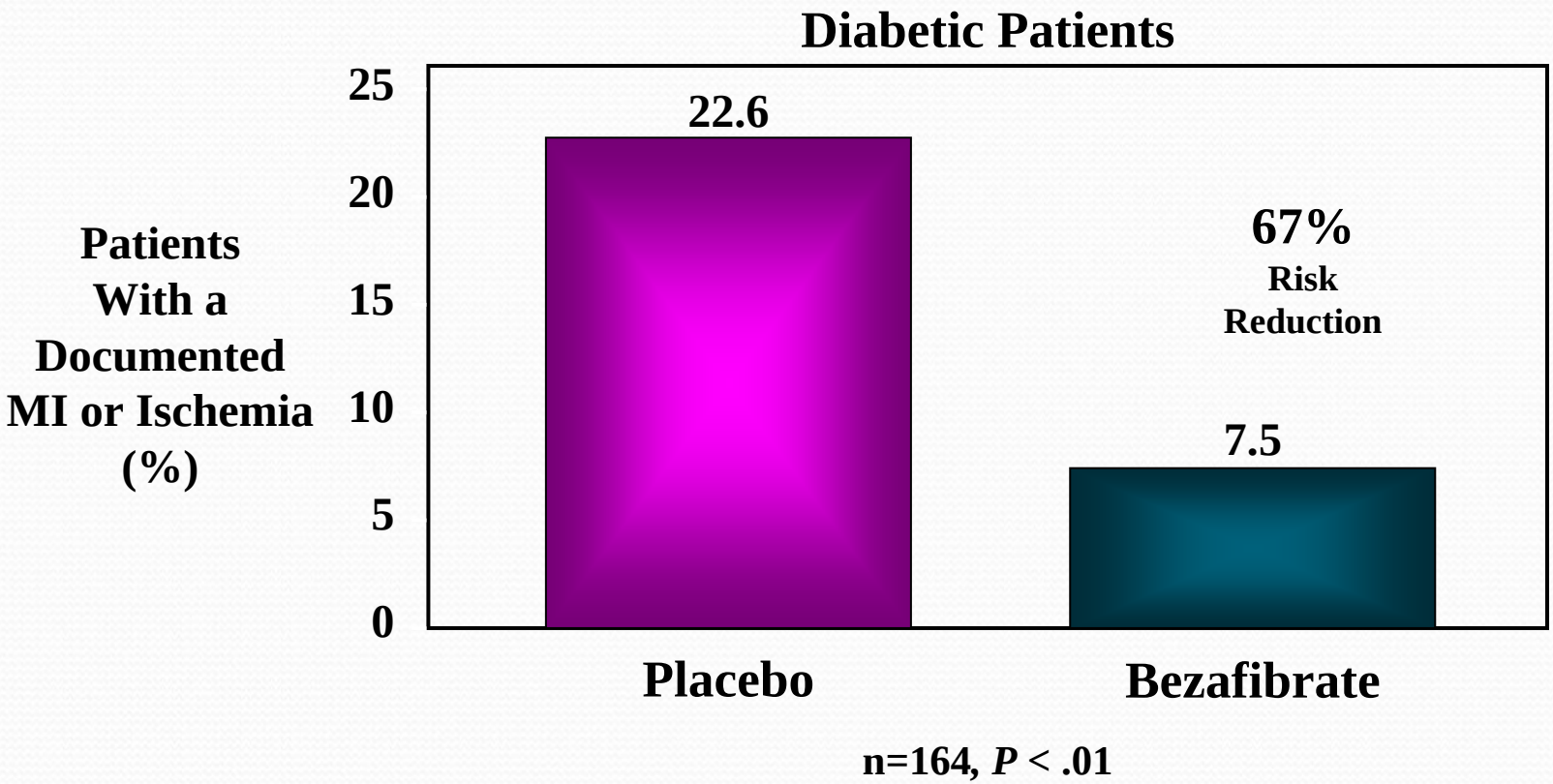
Slower plasma clearance
Greater artery uptake & retention
Faster oxidation
More particles

Helsinki Heart Study Effect of Gemfibrozil on Coronary Events at 5 Years



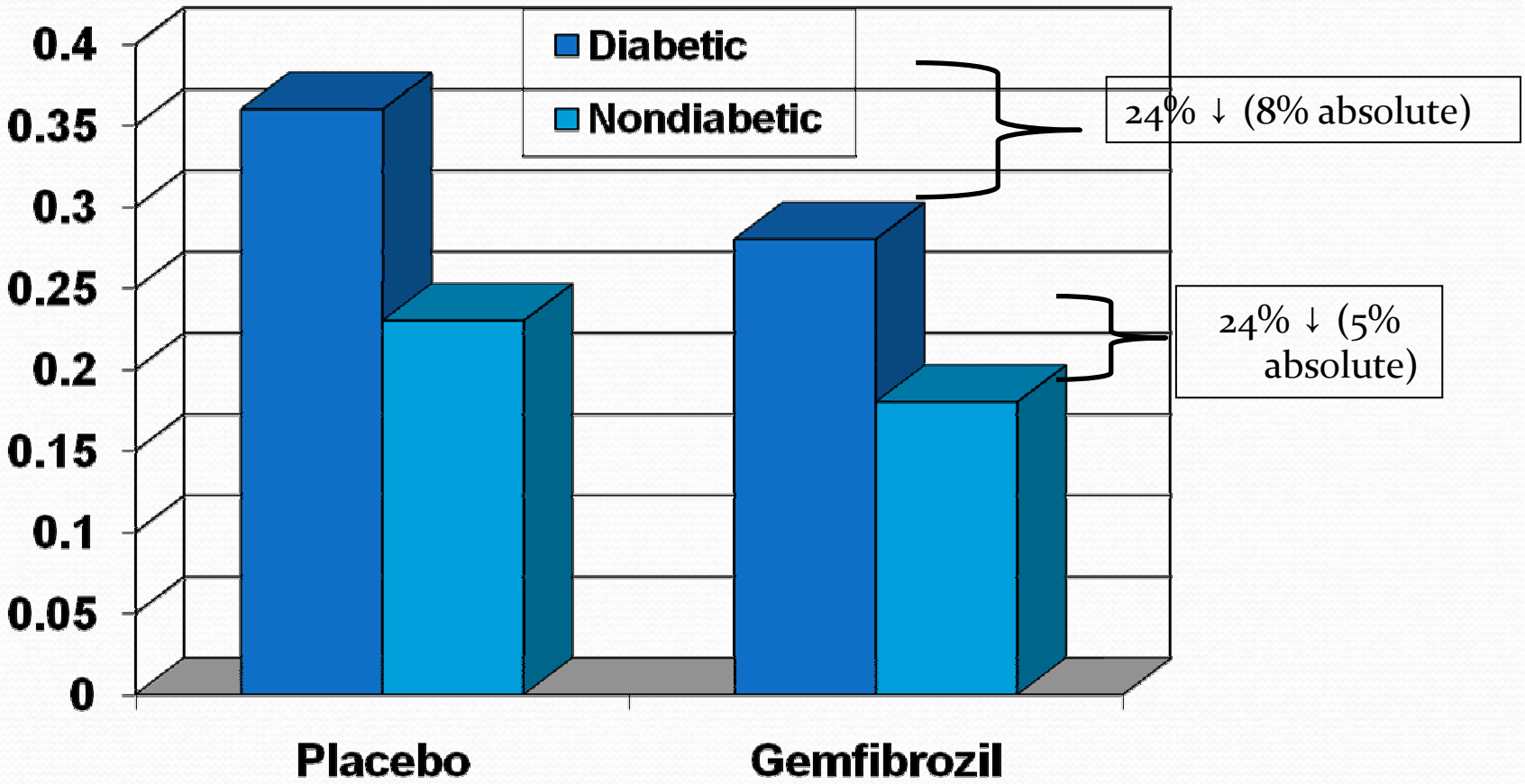
Frick HM et al, N Engl J Med 1987.
Koskinen P et al, Diabetes Care 1992

SENDCAP Study Effect of Bezafibrate on Coronary Events at 5 Years



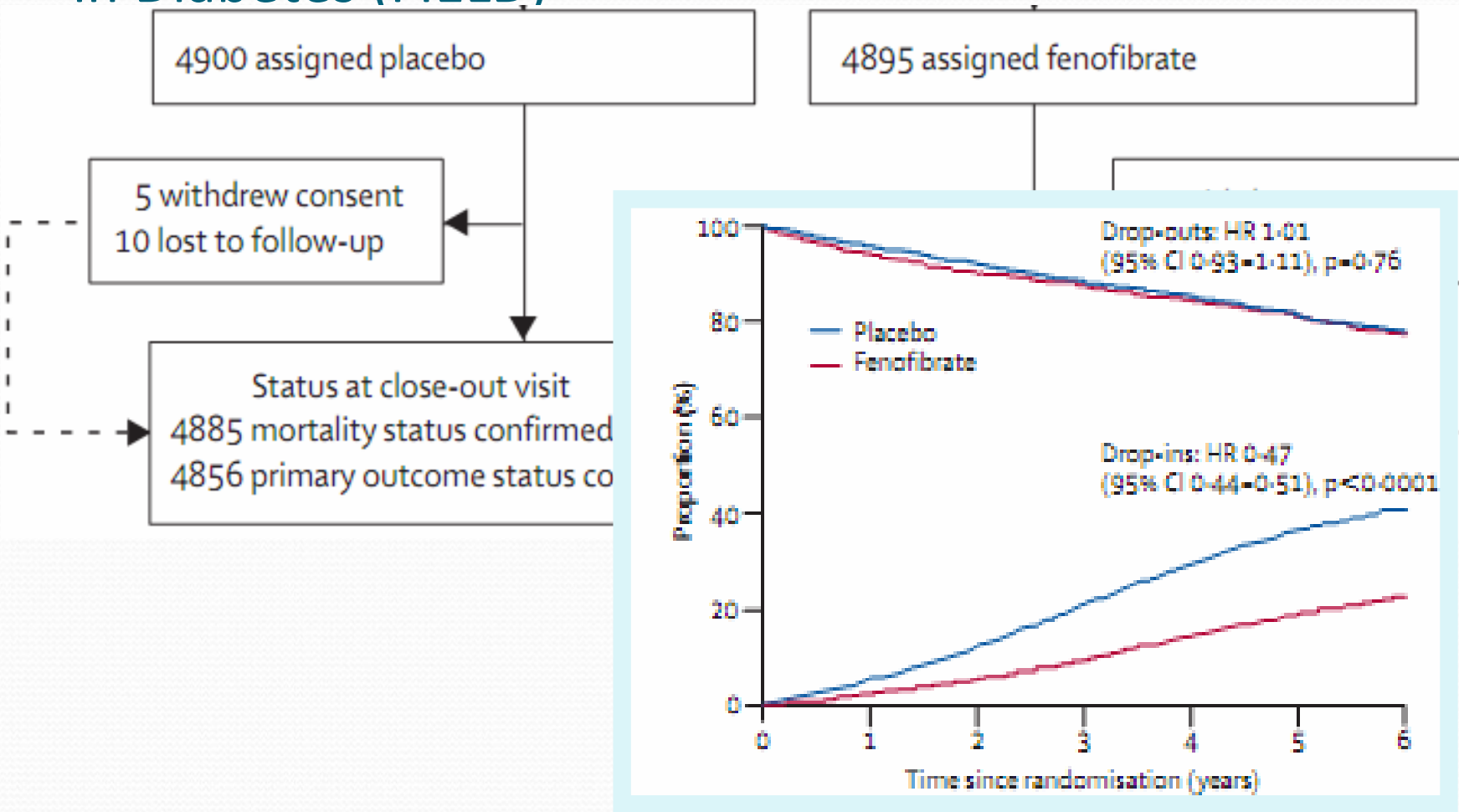
Elkeles RS et al, *Diabetes Care* 1998.

Gemfibrozil : CV Death, Nonfatal MI, and Stroke



VAHIT Study, Rubins et al, N Engl J Med 1999;341:410-8

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)



Lancet 2005; 366: 1849–61

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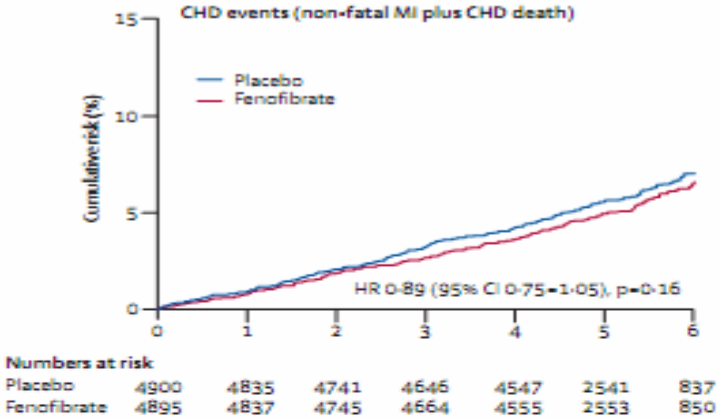
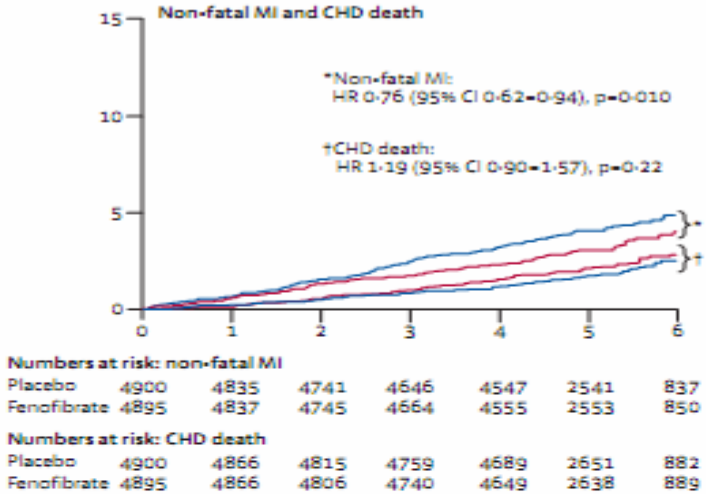
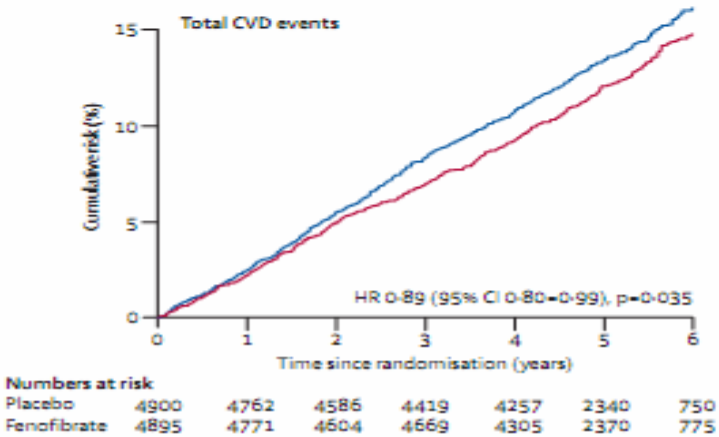
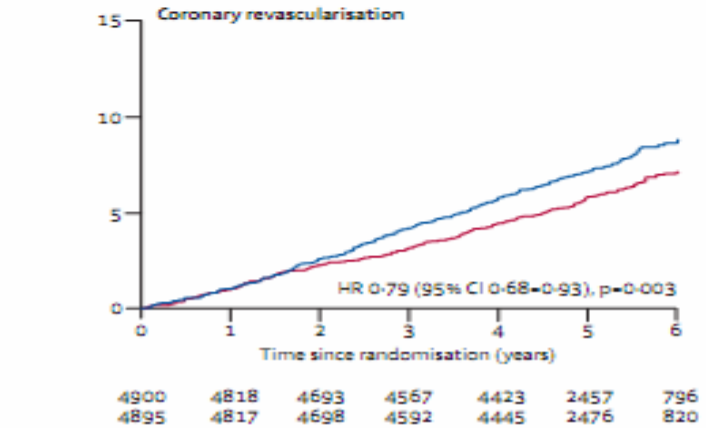








Lancet 2005; 366: 1849–61

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

- Reduction in non-fatal MI, ↑CV mortality
- Reduction in total CVD, revascularization
- Effects on CVD after adjusting for concomitant statins
  - CHD events ↓ 19%: p = 0.01
  - Total CVD events ↓ 15%: p = 0.004
- Risk reduction associated with starting statins
  - CHD: ↓ 49% (p<0.001)
  - CVD: ↓ 26% (p= 0.004)

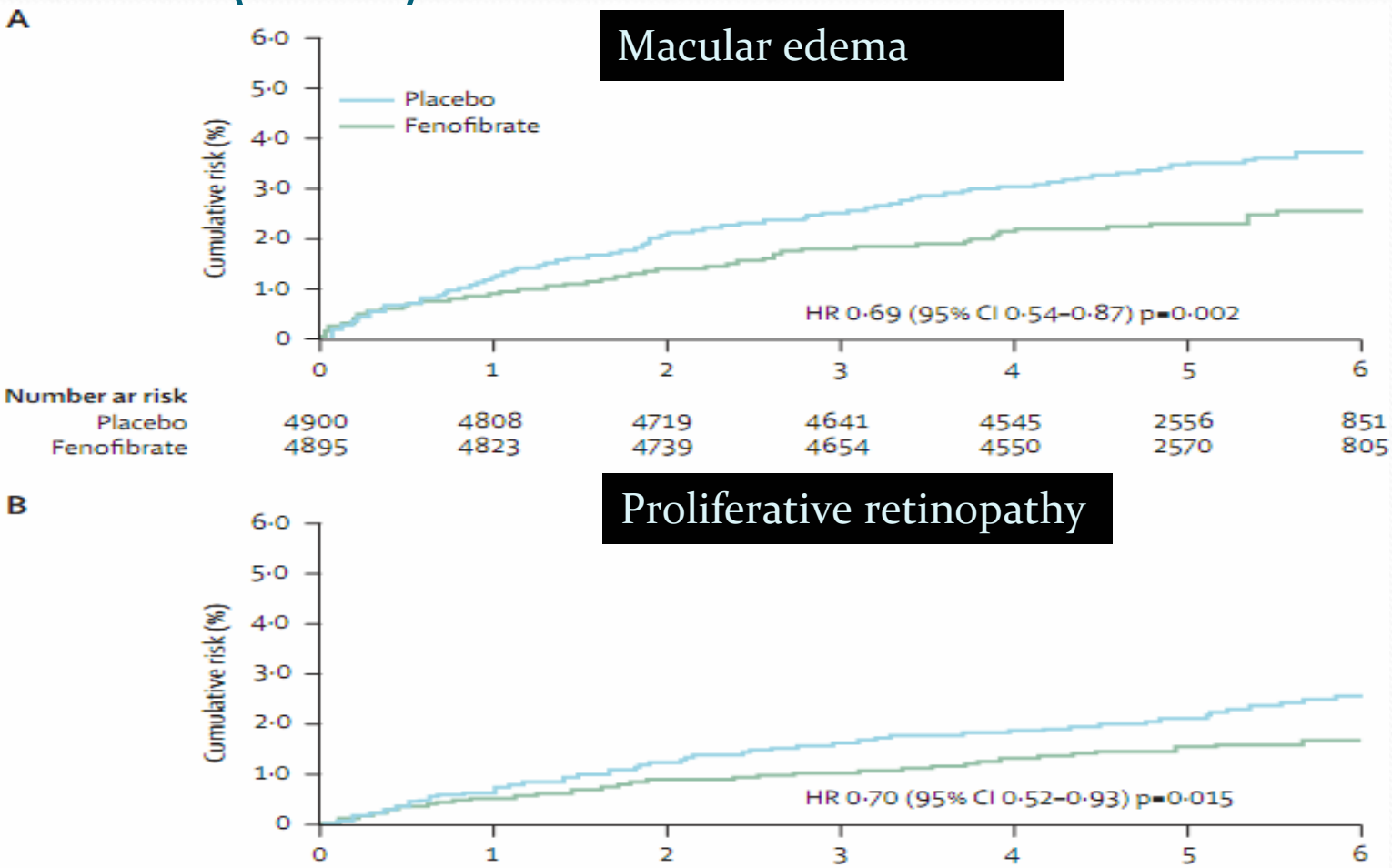
Lancet 2005; 366: 1849–61

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD): renal and eye effects

- 2·6% more patients albuminuria regression or not progressing
- 1.6% fewer patients required laser photocoagulation
- Subset analysis: low HDL group greater benefit, particularly with high triglyceride

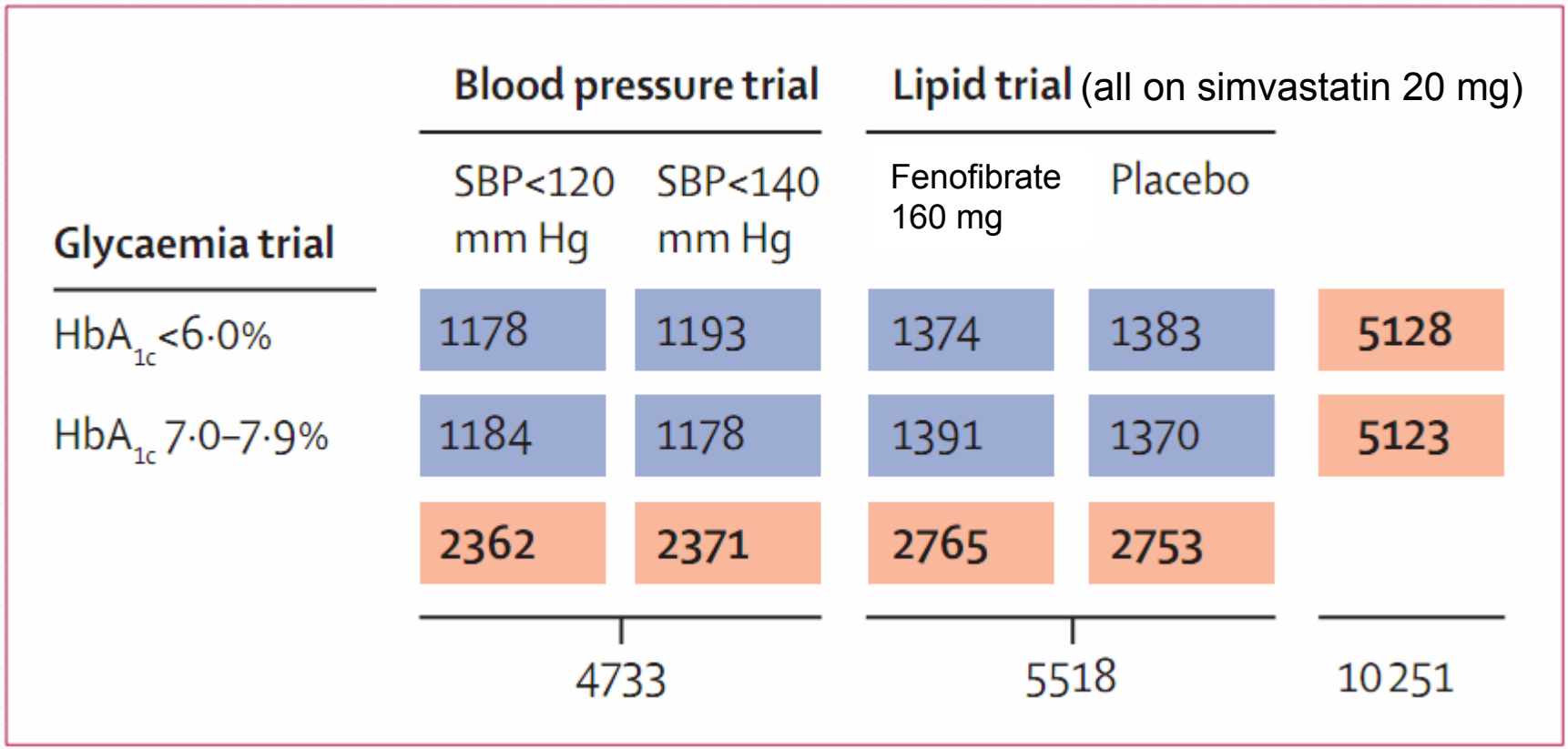
Lancet 2005; 366: 1849–61, Diabetes Care 2009;32:493–498

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)



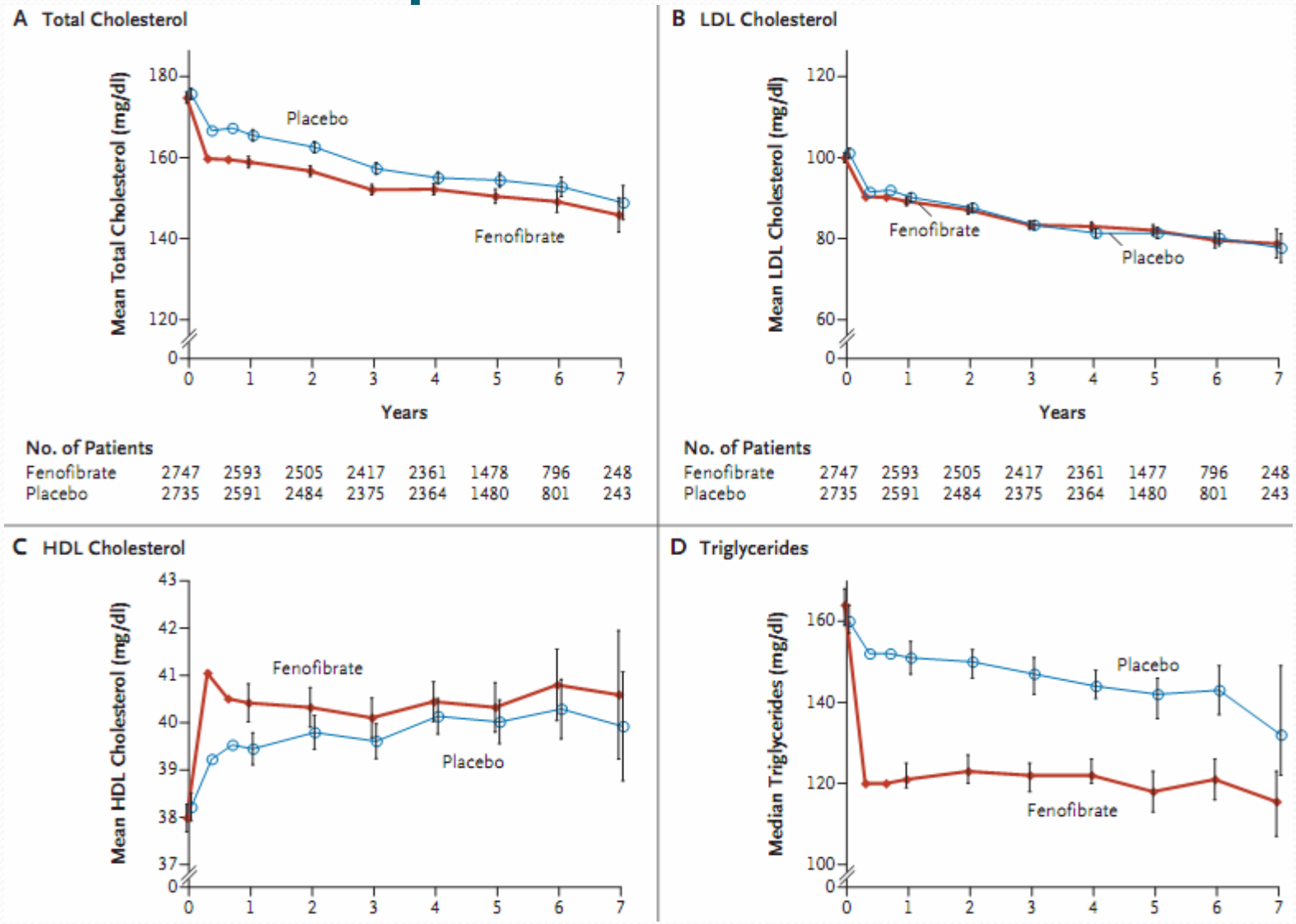
Keech et al. Lancet 2007; 370: 1687–97

ACCORD Randomization: glycemia, blood pressure, lipids



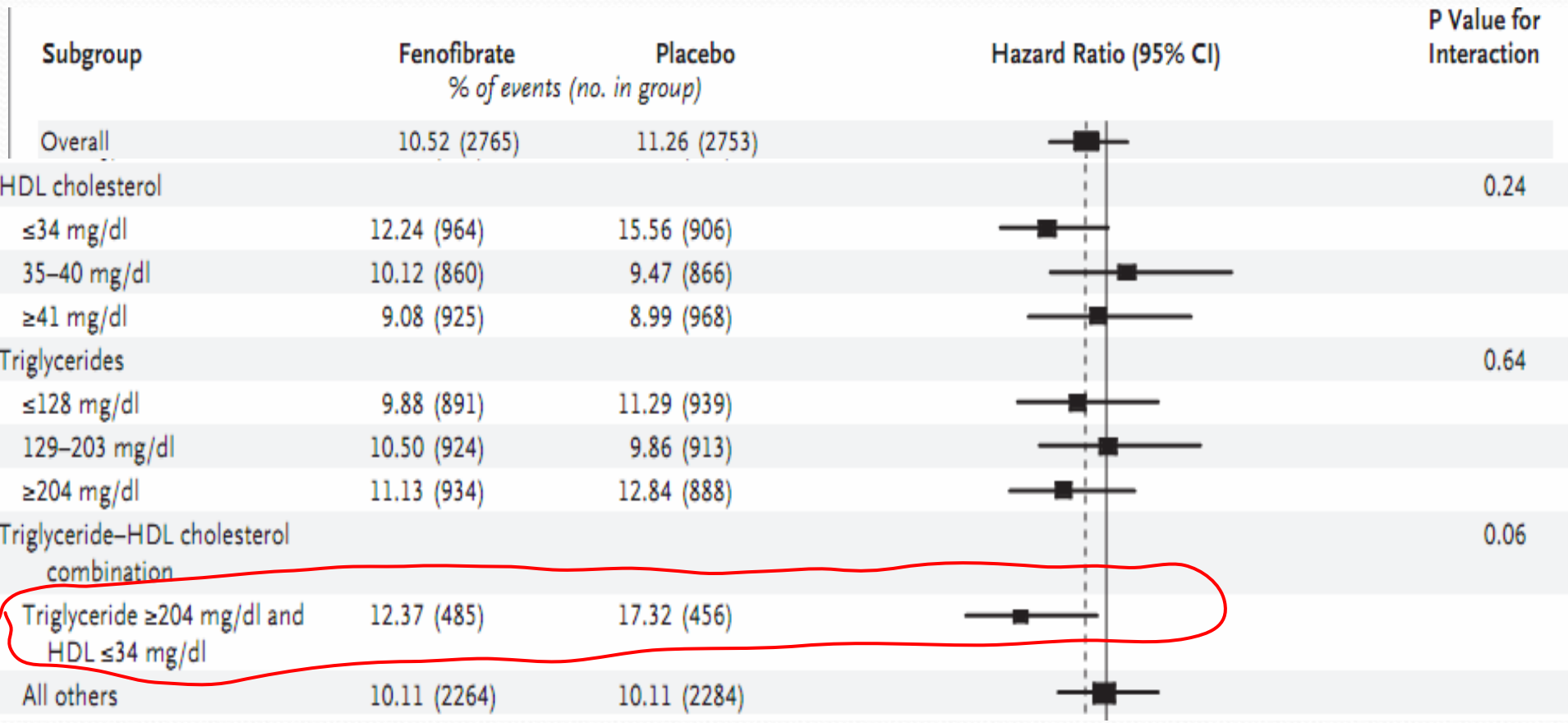
Accord microvascular. Lancet 2010;376:419

ACCORD Lipid Trial



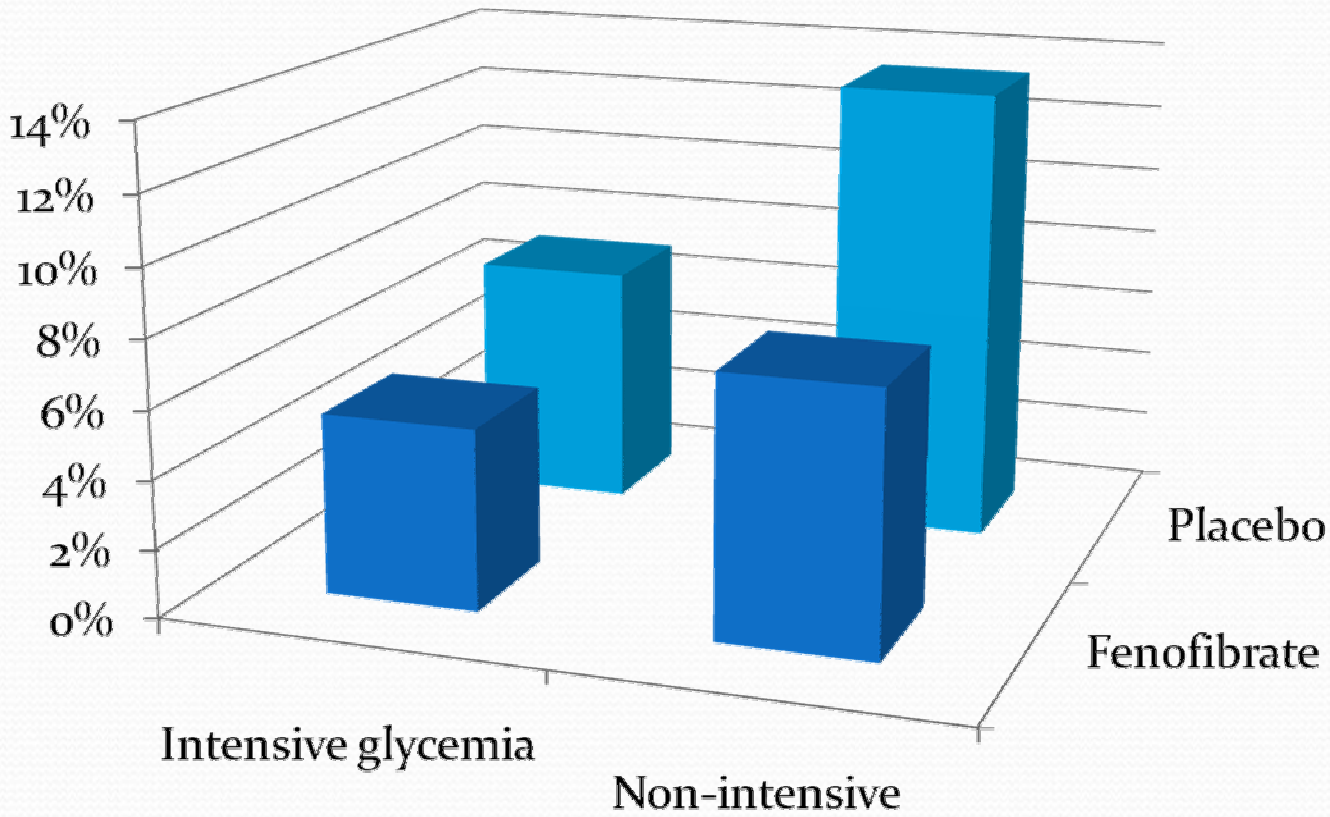
N Engl J Med 2010

ACCORD Lipid: CVD outcomes



N Engl J Med 2010

ACCORD Lipid: Retinopathy Progression



ACCORD Study Group. N Engl J Med. 2010;363:233-4

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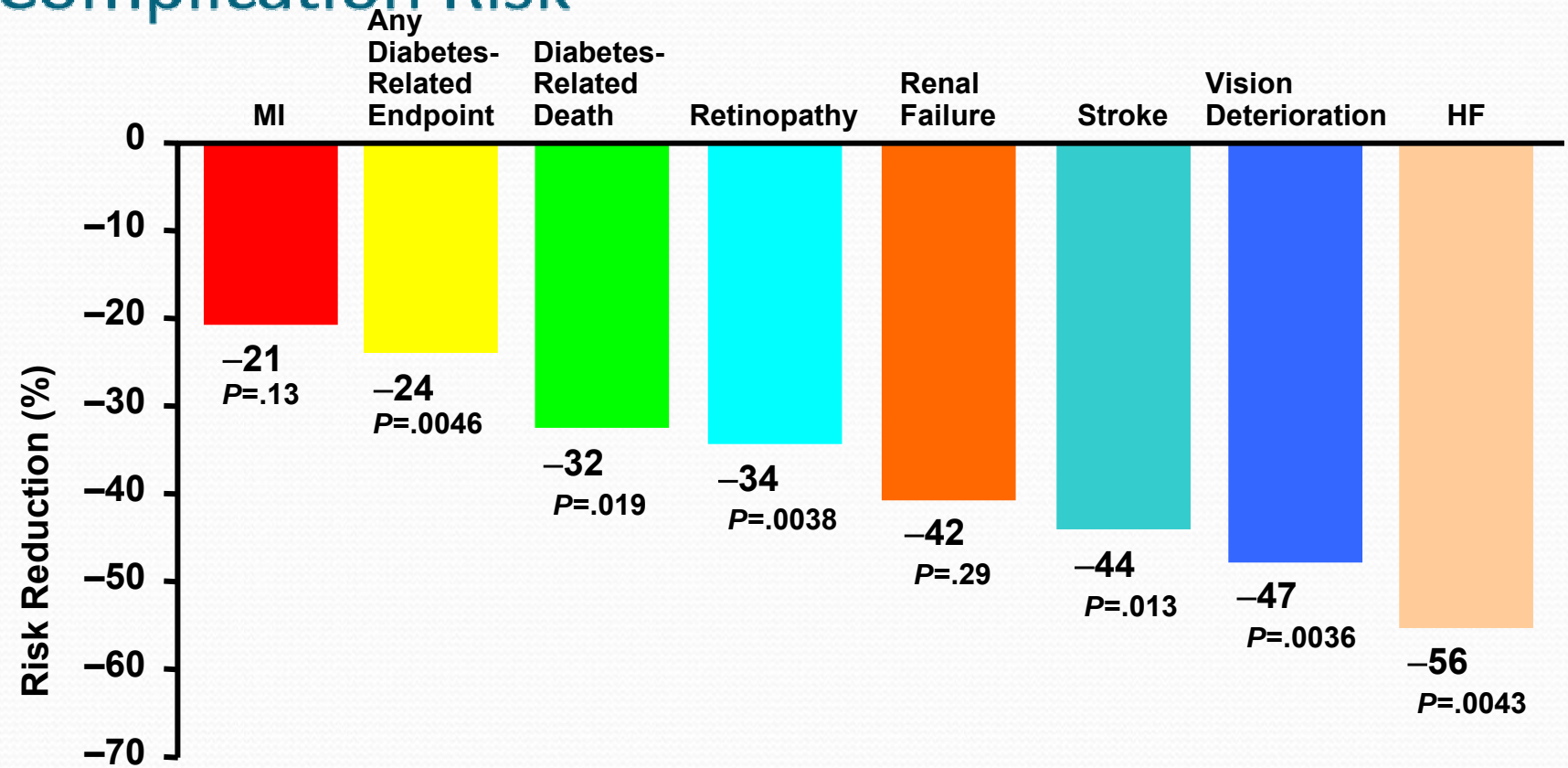
UKPDS: BP substudy – Effect of BP Lowering on Complication Risk

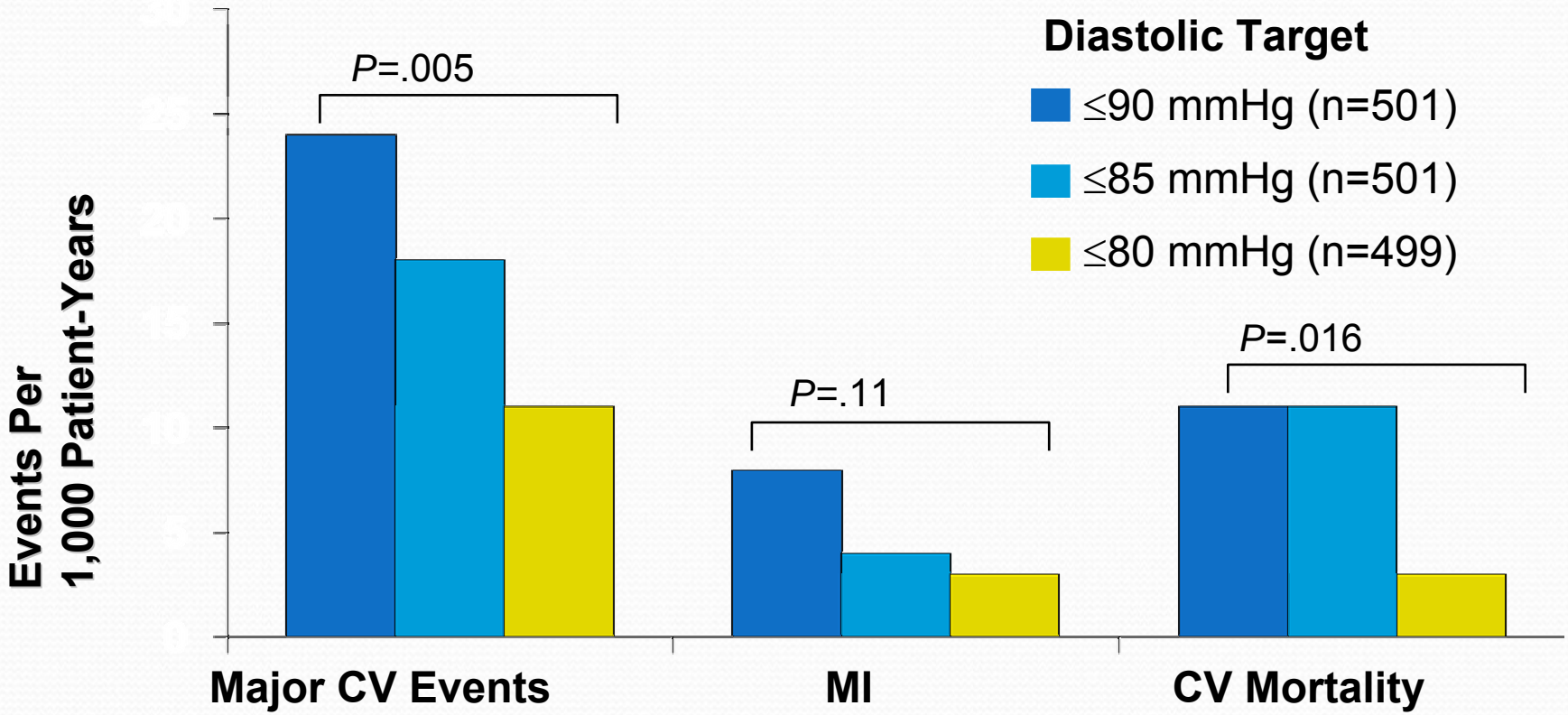


1,148 patients with HTN and type 2 diabetes were allocated to tight (<150/85 mmHg; n=758) or less tight (<180/105 mmHg; n=390) BP control and followed for a median of 8.4 years. Mean BP achieved in tight control group was 144/82 mmHg and 154/87 mmHg for the less tight group.

UKPDS=United Kingdom Prospective Diabetes Study.

UKPDS Group. UKPDS 38. *BMJ.* 1998;317:703–713.

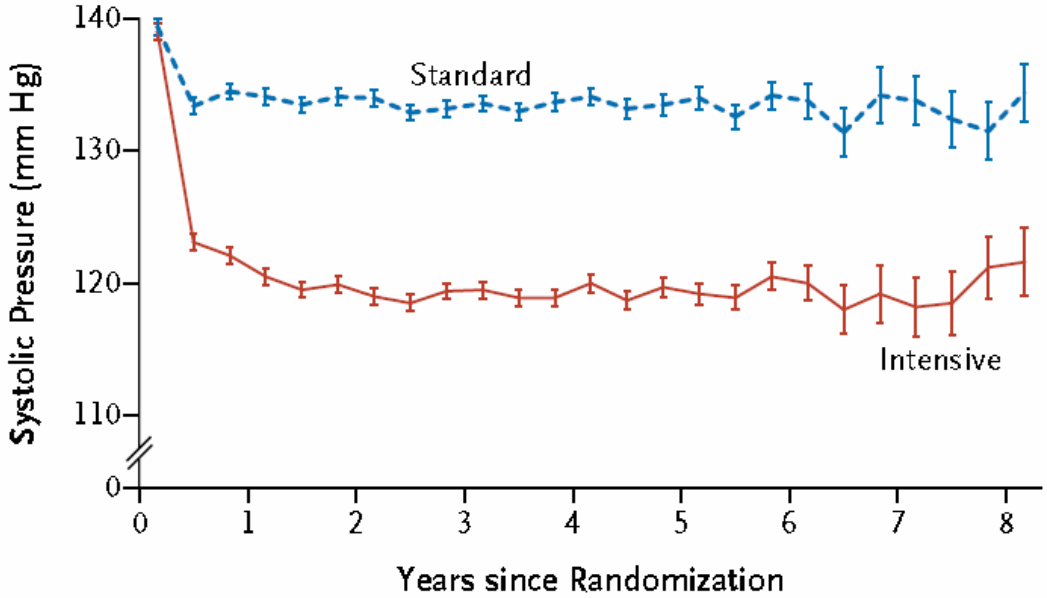
Major Outcomes of the HOT Trial: Diabetes Subgroup



HOT=Hypertension Optimal Treatment. Subgroup of 1,501 patients, mean age 62 years, with HTN and diabetes at baseline were randomized to target DBP of 90, 85, or 80 mmHg—and a low dose of acetylsalicylic acid or placebo. Felodipine was baseline therapy with the addition of ACEIs or β-blockers and diuretics as needed.

Hansson L et al. *Lancet.* 1998;351:1755–1762.

ACCORD blood pressure study



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

ACCORD Study Group. N Engl J Med 2010

ACCORD blood pressure: risks

	N	BP	↓ BP	↓ pulse	↑ K	K<3.2	↑ crea
Stan-dard	2371	133/71	1	3	1	27	367
Inten-sive	2362	119/64	17	12	9	49	561

ACCORD Study Group. N Engl J Med 2010

ACCORD blood pressure: benefit

Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	%/yr	*no. of events*	%/yr		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

ACCORD Study Group. N Engl J Med 2010

ADVANCE 2x2 factorial blood pressure and glycemia intervention

- Glycemic treatment: A1c 7.5% reduced 0.61%
- Perindopril/indapamide: 145/81 reduced 7/3

Blood pressure\Glucose tx	intensive	standard
Perindopril/indapamide	2783	2786
Placebo	2788	2783

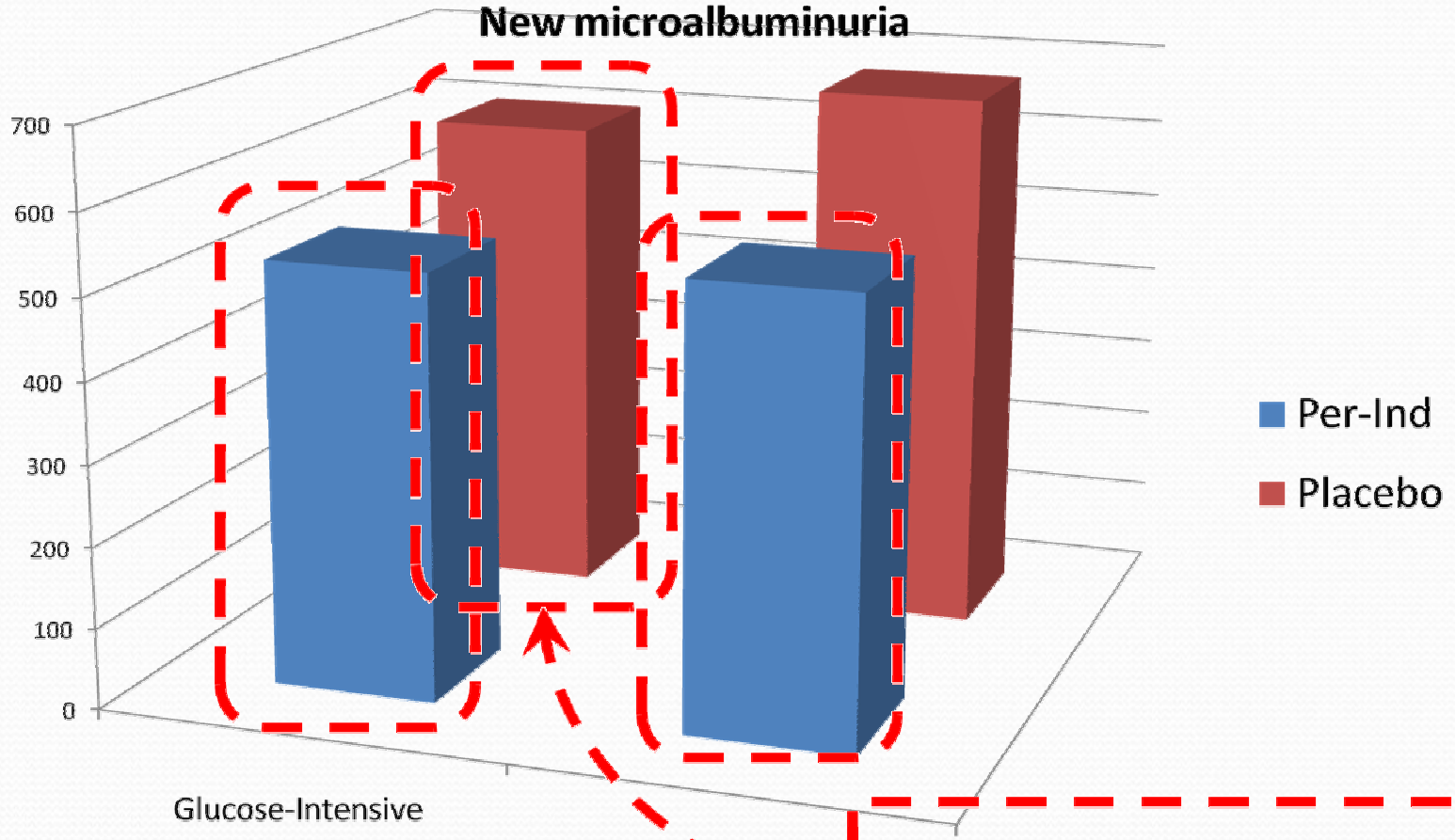
Zoungas et al. Diabetes Care 2009;32:2068

ADVANCE: blood pressure & glycemic treatment

	Randomized treatments				
	Intensive glucose and perindopril-indapamide	Standard glucose and perindopril-indapamide	Intensive glucose and placebo	Standard glucose and placebo	$P_{interaction}$
n	2,783	2,786	2,788	2,783	
Death from any cause					
No. events	198	210	231	240	
HR (95% CI)	0.82 (0.68–0.99)	0.87 (0.72–1.04)	0.96 (0.80–1.15)	1.00 (reference)	0.90
Death from cardiovascular causes					
No. events	104	107	121	136	
HR (95% CI)	0.76 (0.59–0.98)	0.78 (0.60–1.00)	0.89 (0.70–1.14)	1.00 (reference)	0.62
Major coronary heart events					
No. events	133	132	139	155	
HR (95% CI)	0.92 (0.77–1.10)	0.87 (0.73–1.04)	0.90 (0.71–1.13)	1.00 (reference)	0.47
Major cerebrovascular events					
No. events	111	104	111	107	
HR (95% CI)	1.03 (0.79–1.35)	0.96 (0.73–1.26)	1.03 (0.79–1.35)	1.00 (reference)	0.85
All renal events					
No. events	590	630	686	777	
HR (95% CI)	0.72 (0.65–081)	0.77 (0.69–0.85)	0.88 (0.79–0.97)	1.00 (reference)	0.33
New or worsening nephropathy					
No. events	81	100	96	120	
HR (95% CI)	0.67 (0.50–0.88)	0.82 (0.63–1.07)	0.80 (0.61–1.05)	1.00 (reference)	0.93
New or worsening retinopathy					
No. events	147	142	133	153	
HR (95% CI)	0.96 (0.76–1.20)	0.92 (0.73–1.16)	0.86 (0.69–1.09)	1.00 (reference)	0.27
New onset of microalbuminuria					
No. events	525	542	605	673	
HR (95% CI)	0.75 (0.67–0.84)	0.77 (0.68–0.86)	0.90 (0.80–100)	1.00 (reference)	0.29
New onset of macroalbuminuria					
No. events	44	74	73	95	
HR (95% CI)	0.46 (0.32–0.65)	0.77 (0.56–1.04)	0.77 (0.57–1.04)	1.00 (reference)	0.30

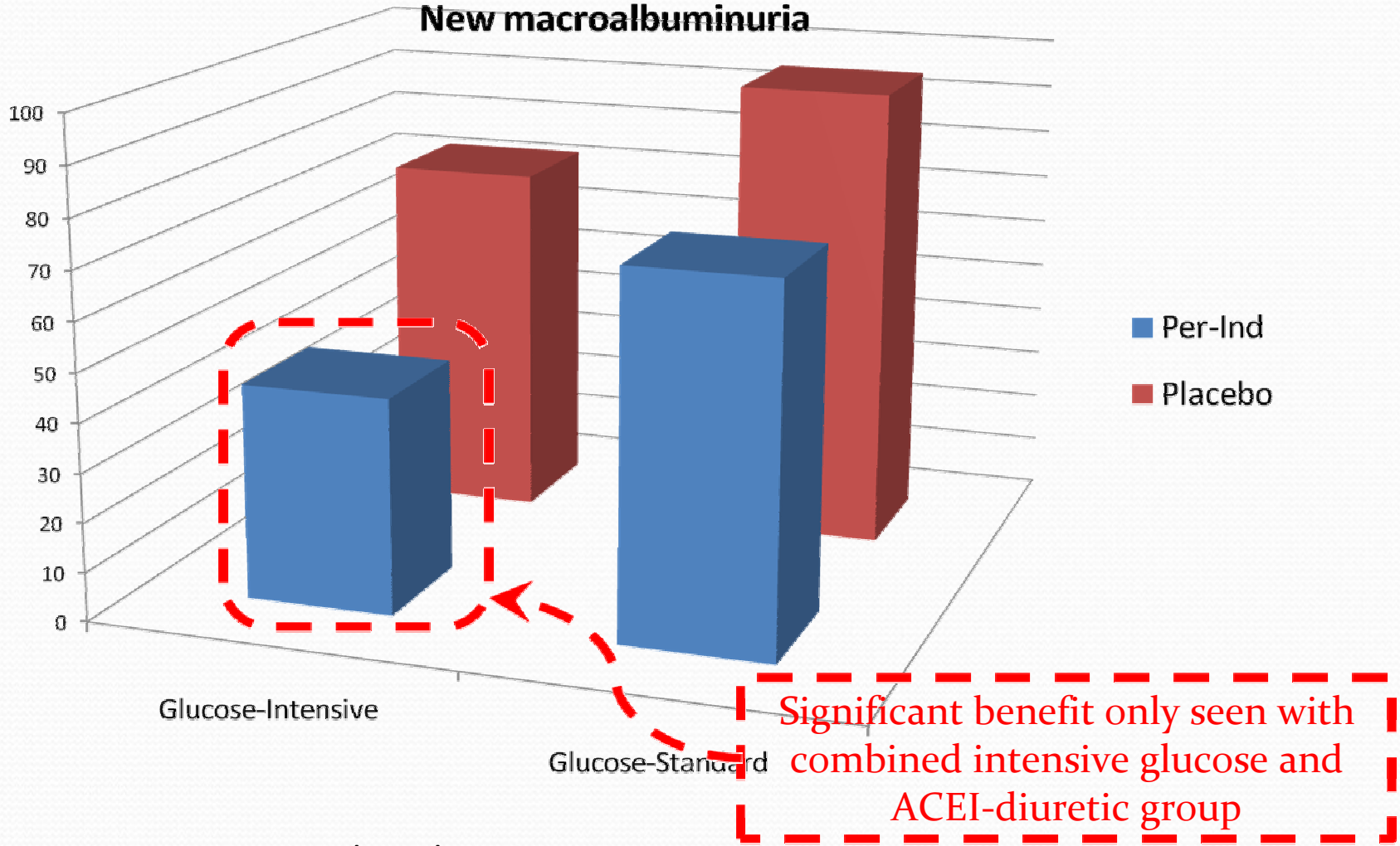
Zoungas et al. Diabetes Care 2009;32:2068

ADVANCE: outcomes



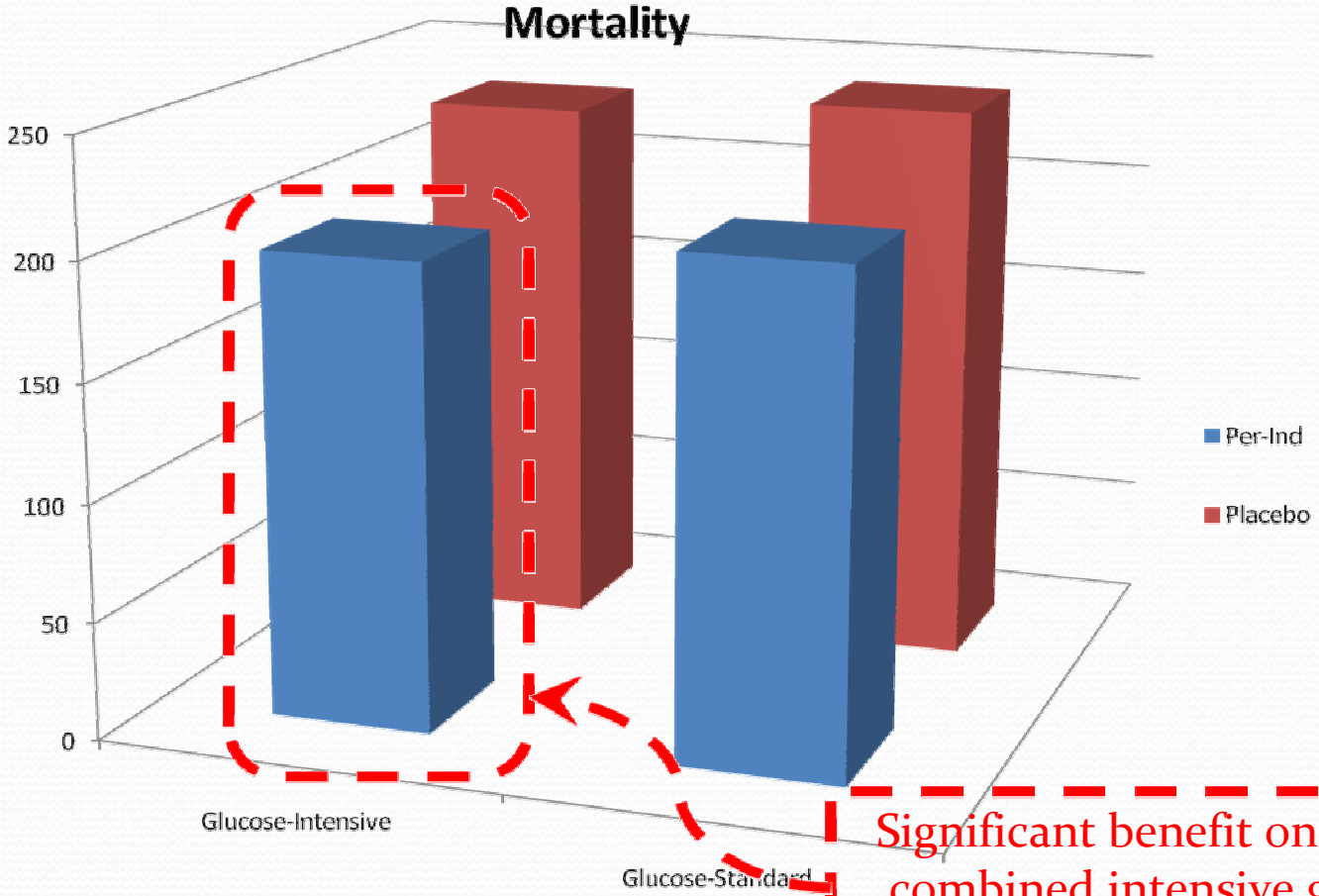
Zoungas et al. Diabetes Care 2009;32:2068

ADVANCE: outcomes



Zoungas et al. Diabetes Care 2009;32:2068

ADVANCE: outcomes



Significant benefit only seen with combined intensive glucose and ACEI-diuretic group

Zoungas et al. Diabetes Care 2009;32:2068

Update on Diabetes - 2010

- Diabetes epidemiology
- ACCORD glycemia: further understanding of outcome
  - Hypoglycemia effect
  - Different A1c-outcome relationship of standard vs. intensive arms
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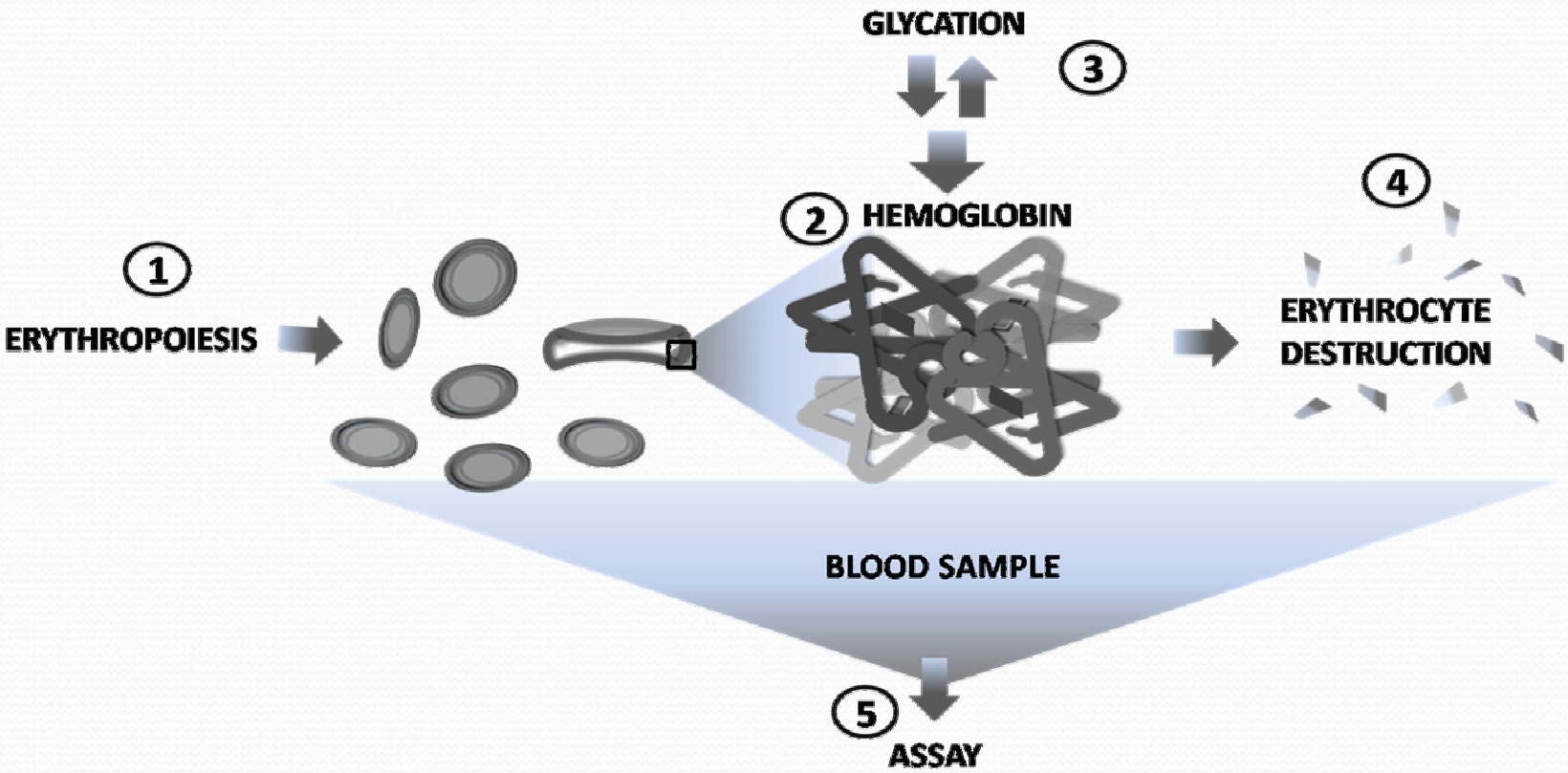
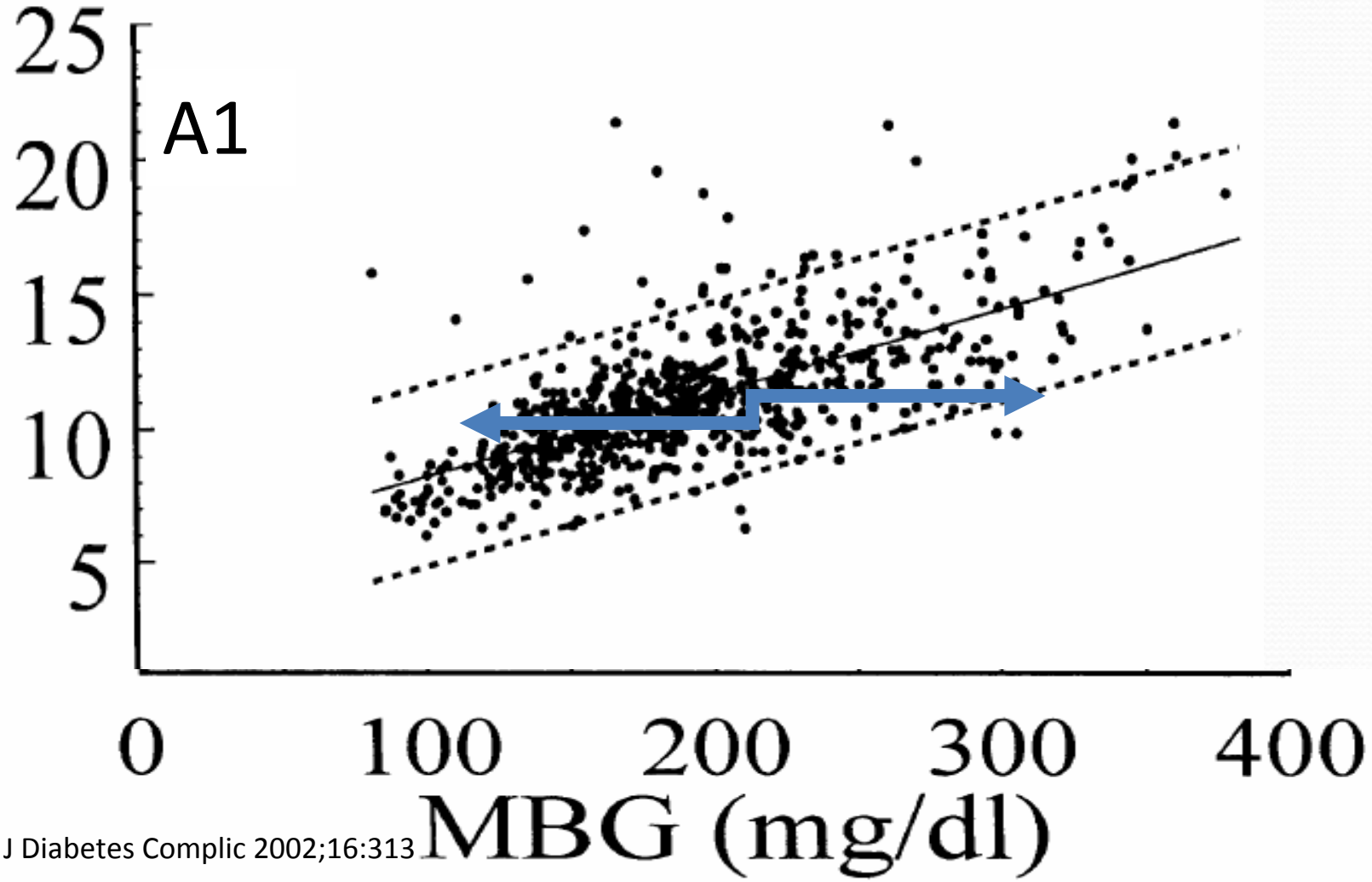
Factors influencing A1c



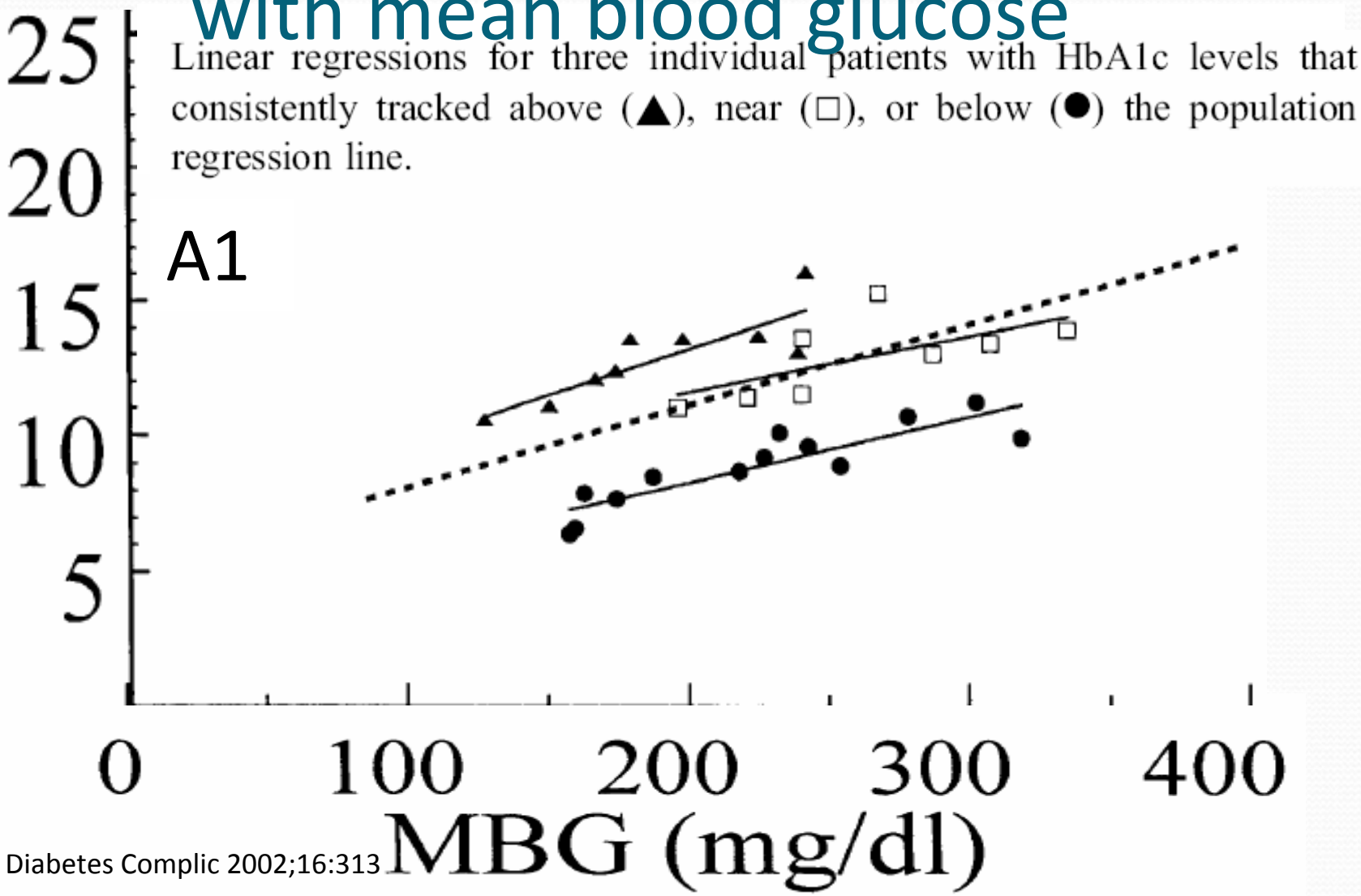
Gallagher, Le Roith, Bloomgarden. J Diabetes 2009;1:9

Correlation of hemoglobin glycation with mean blood glucose



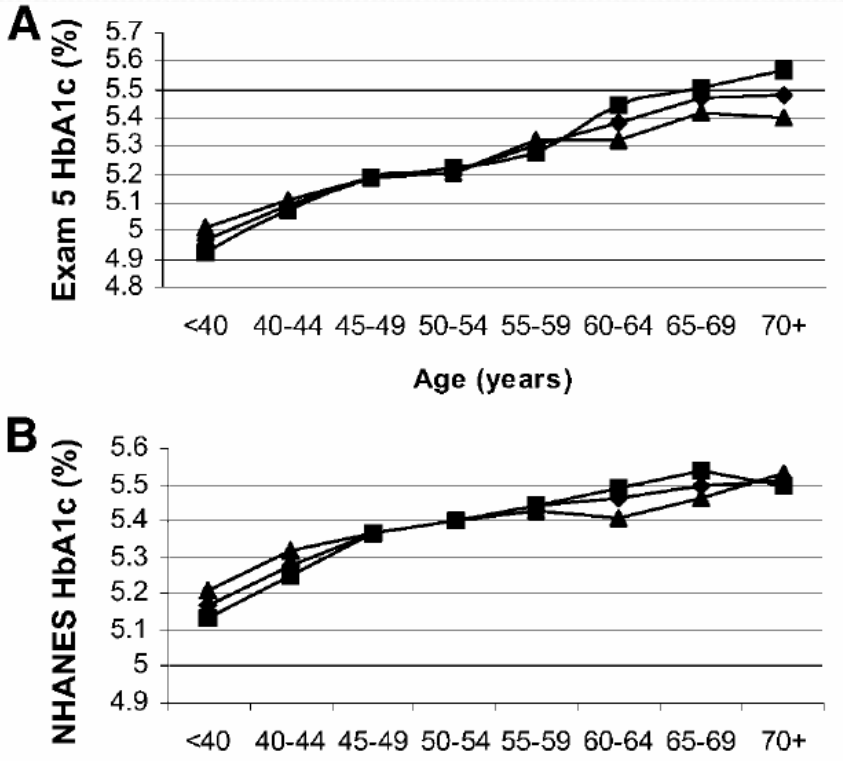
J Diabetes Complic 2002;16:313

Correlation of hemoglobin glycation with mean blood glucose



J Diabetes Complic 2002;16:313

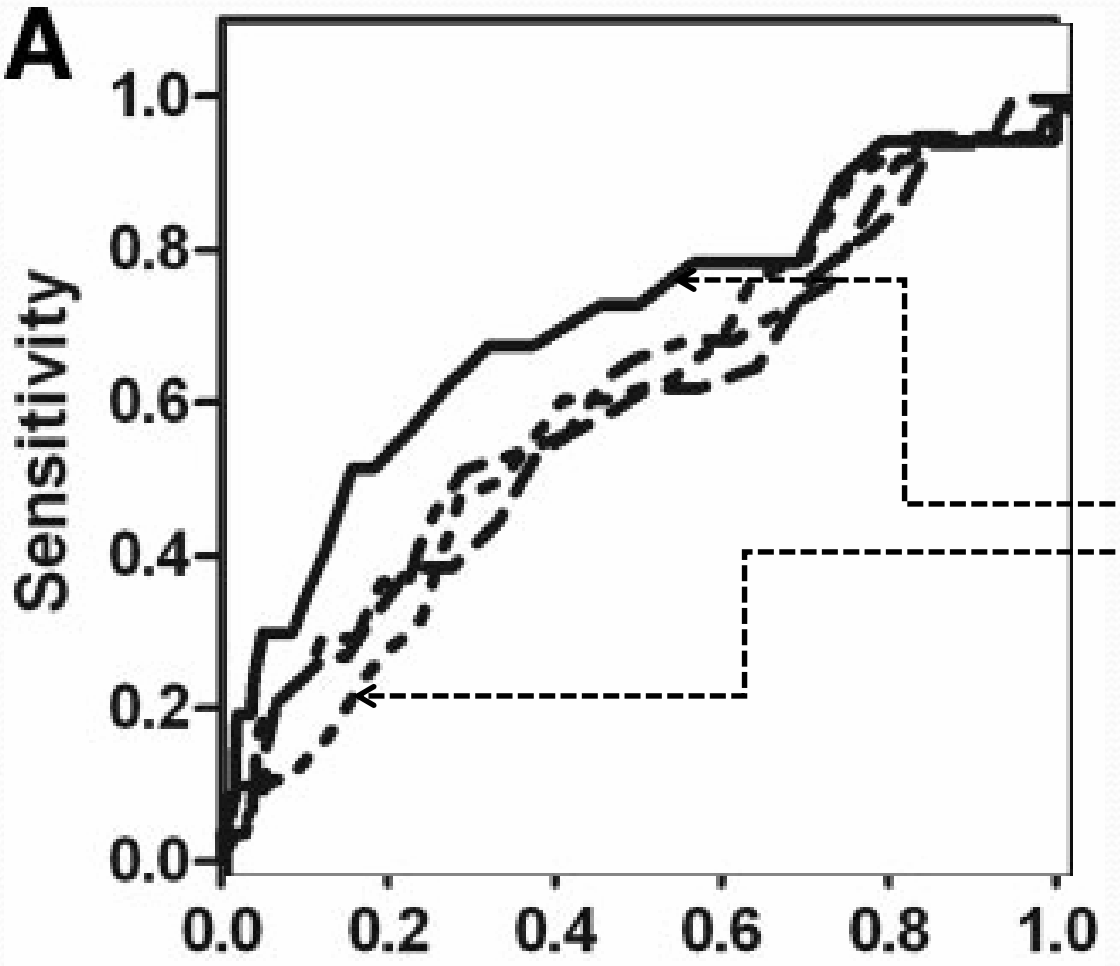
Age vs. A1c



- "In [Framingham and NHANES] nondiabetic and NGT populations, the relationship between age and A1C remained … adjusting for sex, BMI, fasting glucose, and 2-h postload glucose."

Pani et al, Diabetes Care 2008; 31:1991

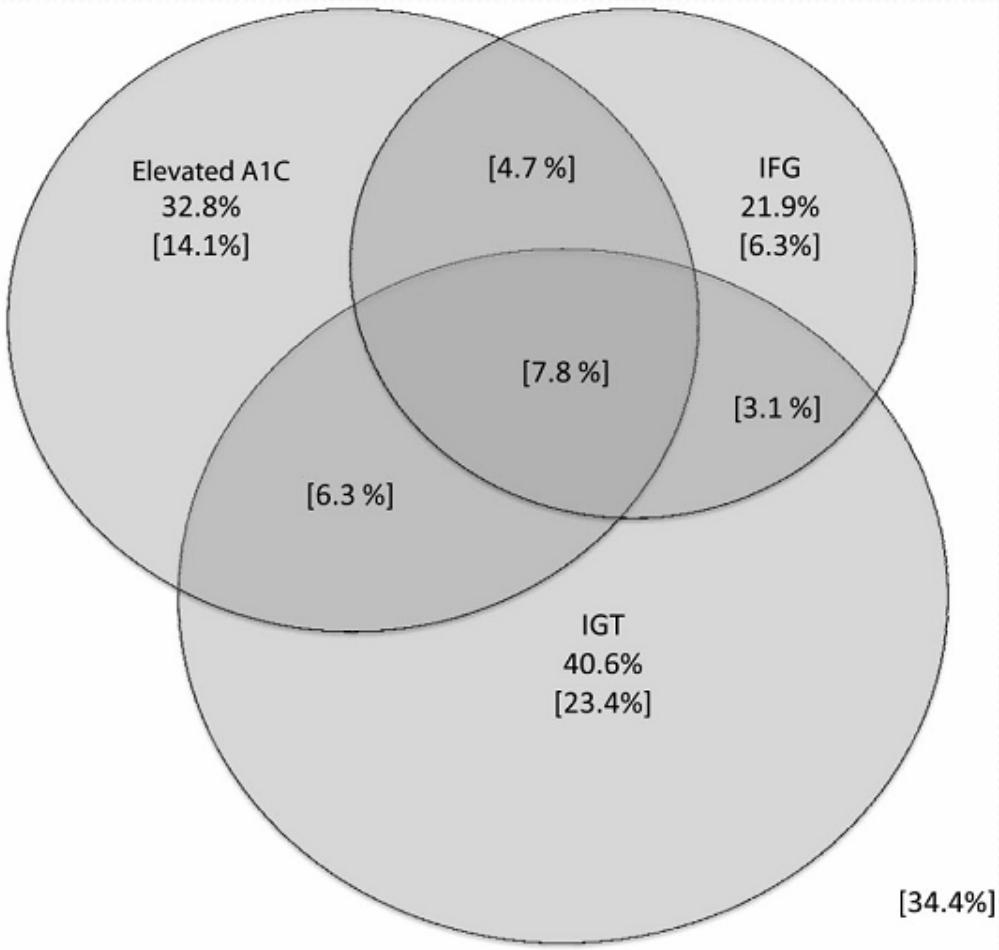
Diagnostic Criteria for Diabetes: use of A1c 6.5%?



Rancho Bernardo Study: Kramer Diabetes Care 2010;33:101-3

64 persons developing diabetes over 10 yr: Baseline prevalence of A1c 5.7-6.4, FBG 100-125, 2hBG 140-199

Prospective study: 593 Finns, born 1935, from 1996-2008.



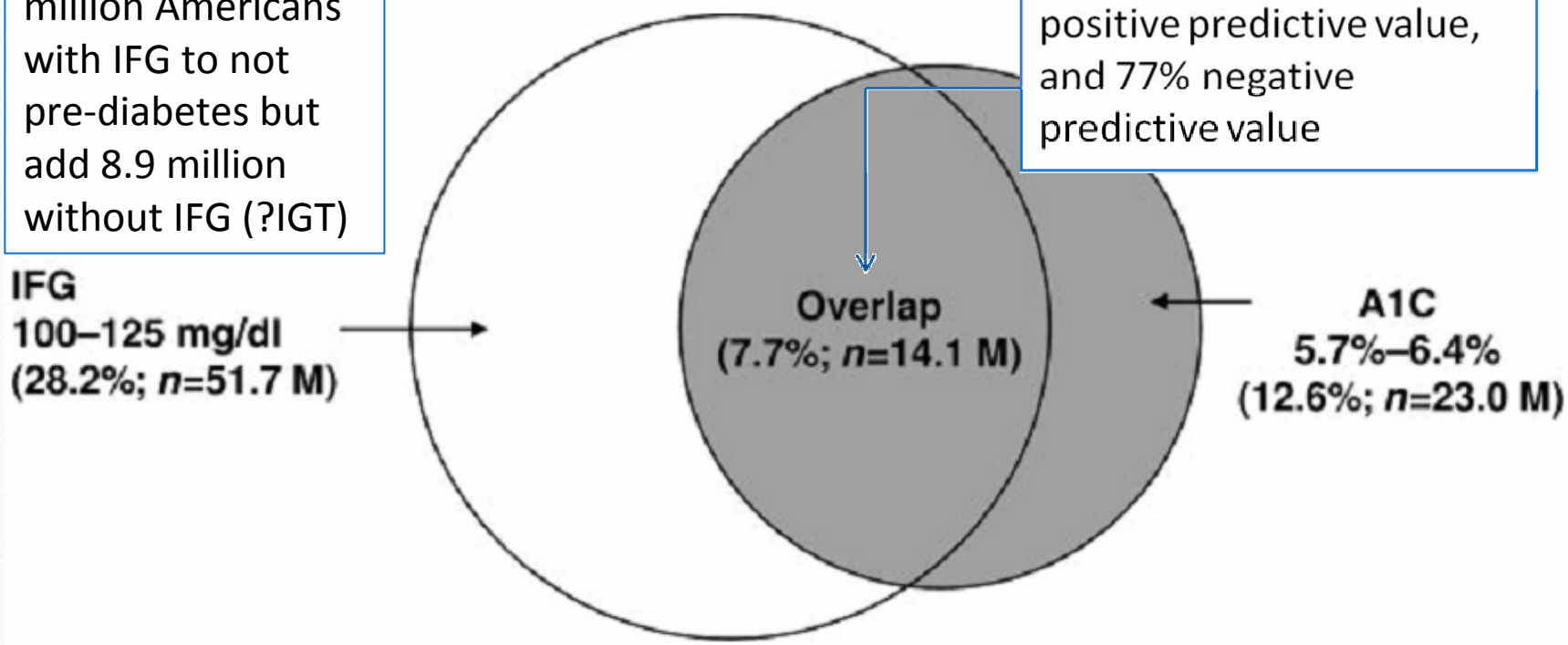
No baseline glycemic abnormality

Cederberg et al. Diabetes Care 2010;33:2077

Overlap of pre-diabetes by IFG and A1C in NHANES among U.S. adults with

A1C alone would reclassify 37.6 million Americans with IFG to not pre-diabetes but add 8.9 million without IFG (?IGT)

Using IFG as reference, pre-diabetes by A1C has 27% sensitivity, 93% specificity, 61% positive predictive value, and 77% negative predictive value



Mann et al. Diabetes Care 2010;33:2190

AACE STATEMENT ON USE OF A1c FOR DIAGNOSIS OF DIABETES

- A1c an … optional …criterion, not primary
- Use traditional glucose criteria when feasible
- Do not use A1c for DM1 or GDM
- A1C may be misleading in ethnic populations (for example, African American patients).
- A1C may be misleading … hemoglobinopathy, Fe deficiency, hemolysis, thalassemia… hepatic, renal disease
- Use standardized, validated A1c assays

Endocrine Practice 2010; 16:155-6

Diabetologia
DOI 10.1007/s00125-008-1027-7

FOR DEBATE

The proposed terminology 'A_{1c}-derived average glucose' is inherently imprecise and should not be adopted

Z. T. Bloomgarden · S. E. Inzucchi · E. Karnieli · D. Le Roith

Received: 15 March 2008 / Accepted: 20 March 2008
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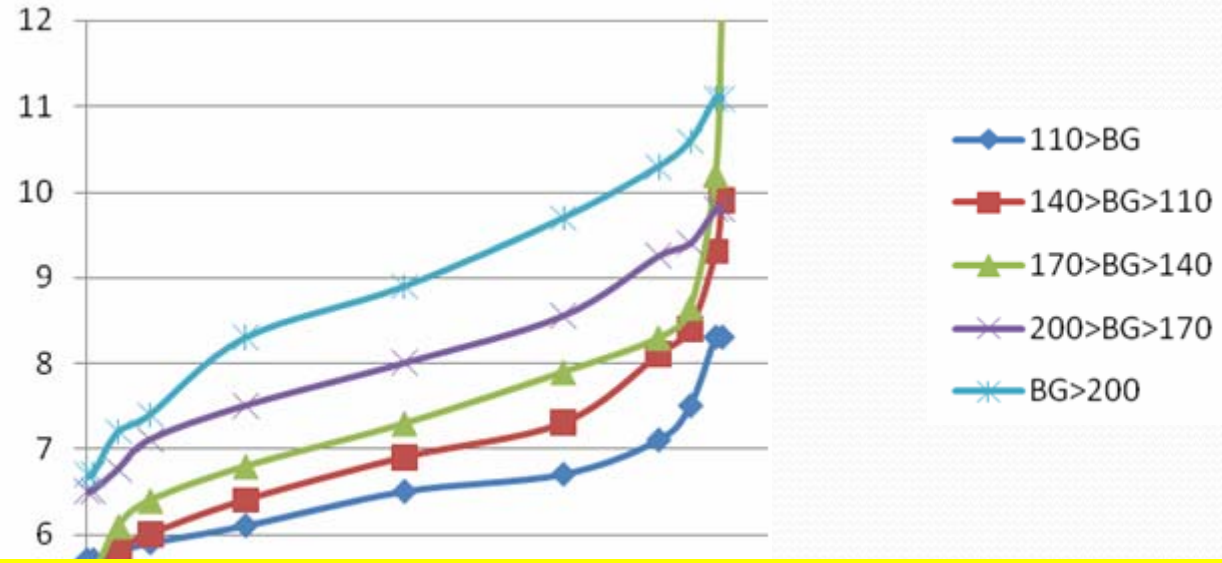
Frequency analysis: Glucose grouping vs. A1c

N=623 insulin treated DM2:
7 point SMBG x 3 d vs. A1c

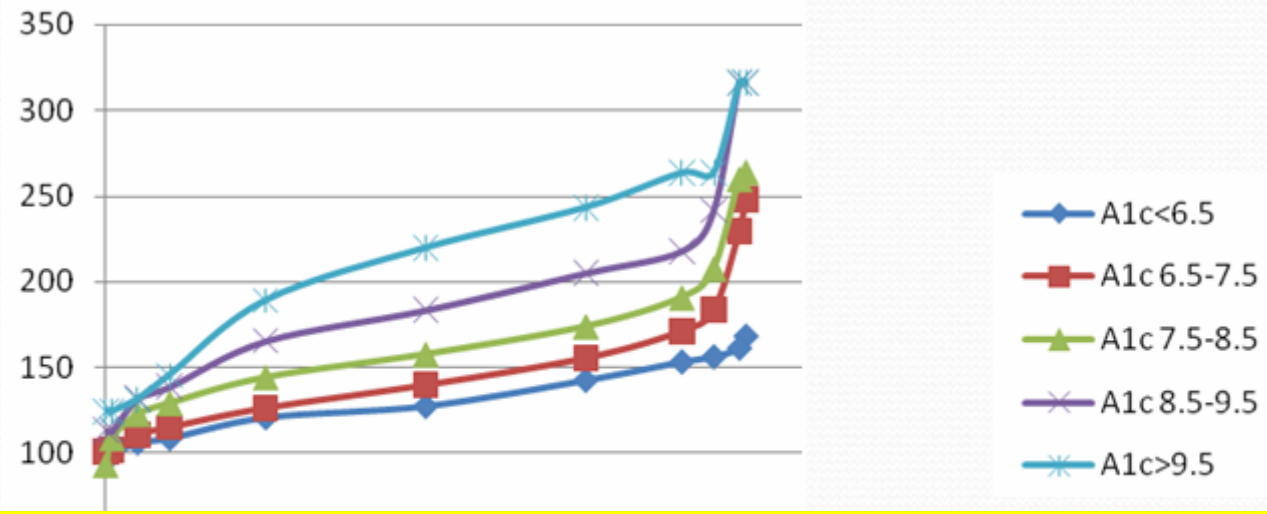


224 patients with MPG 110-140 mg/dl:
10% had A1c <6.0 %
10% had A1c > 8.1%

Shrom, Choi, Ilag, Bloomgarden, Journal of Diabetes, 2010

Frequency analysis: A1c grouping vs. mean glucose

N=623 insulin treated DM2:
7 point SMBG x 3 d vs. A1c



260 patients with A1c 6.5-7.5%:
10% had MPG < 115 mg/dl
10% had MBG > 171 mg/dl

Shrom, Choi, Ilag, Bloomgarden, Journal of Diabetes, 2010

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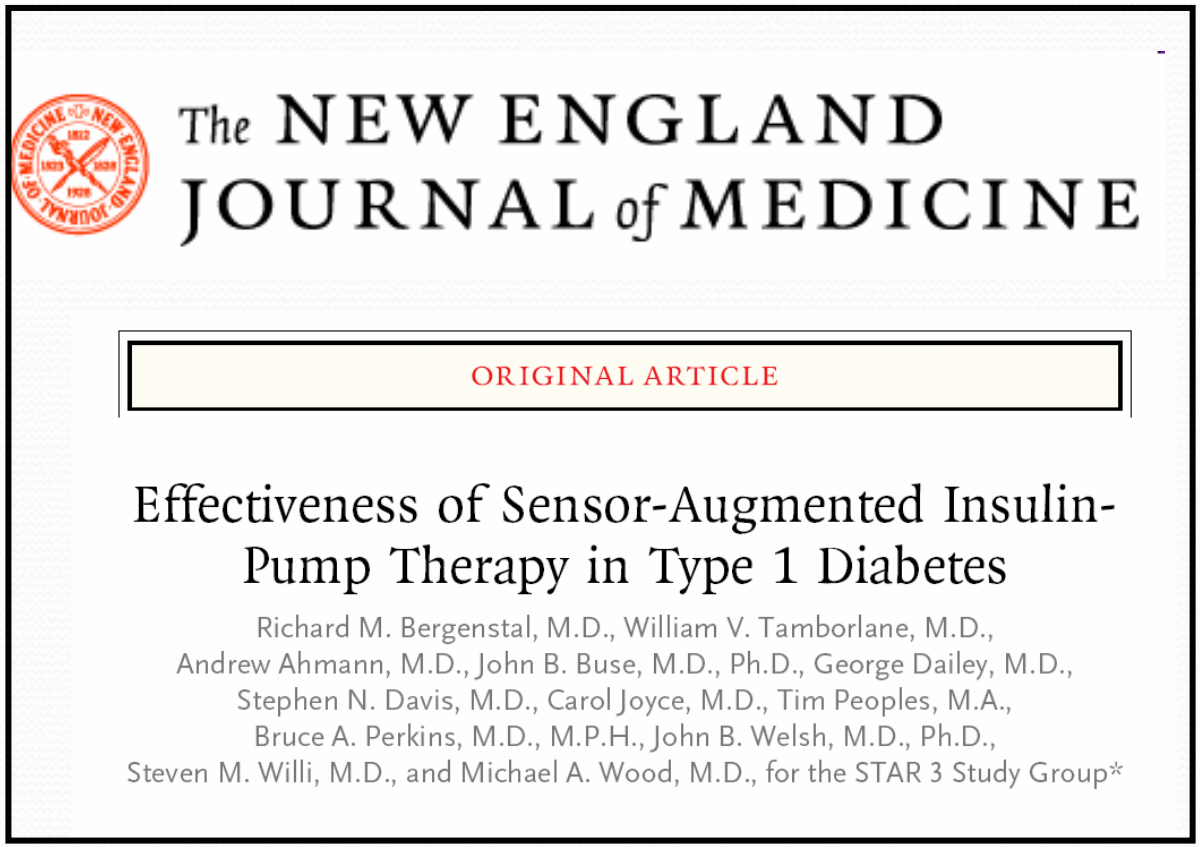


The NEW ENGLAND JOURNAL of MEDICINE

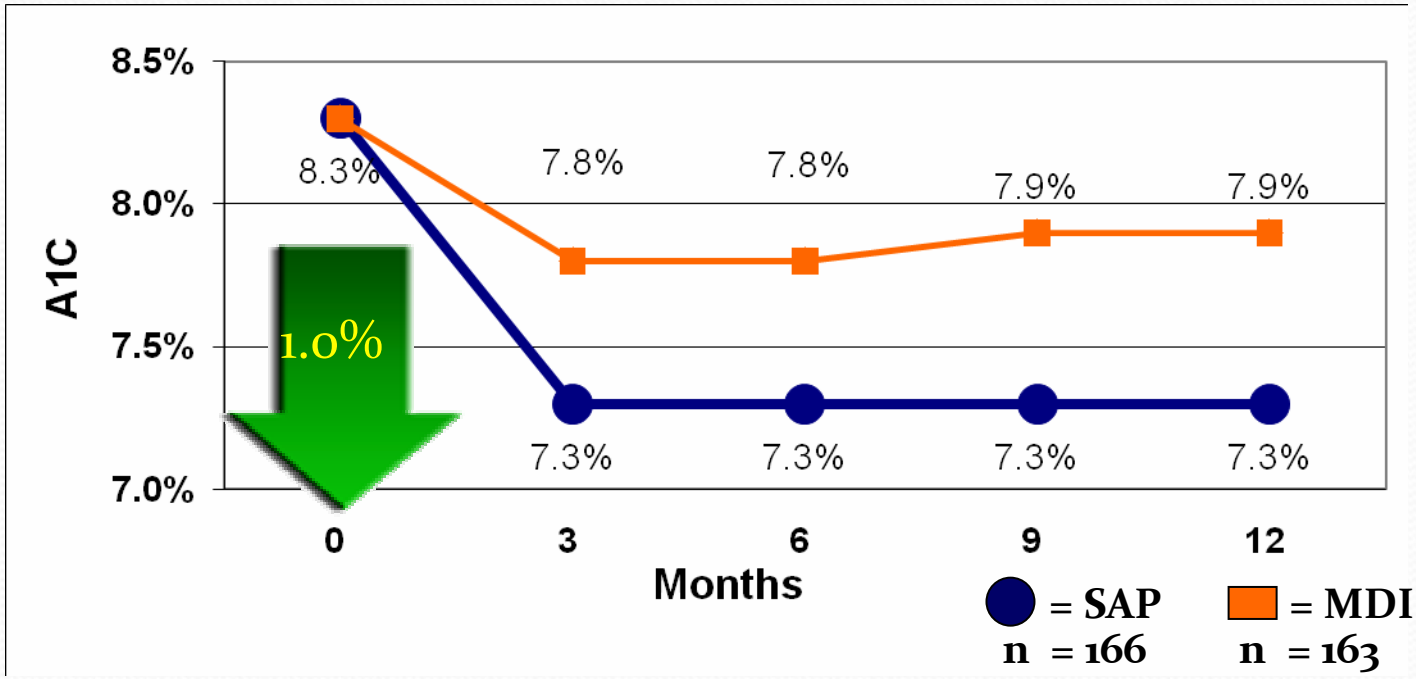
ORIGINAL ARTICLE

Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes

Richard M. Bergenstal, M.D., William V. Tamborlane, M.D., Andrew Ahmann, M.D., John B. Buse, M.D., Ph.D., George Dailey, M.D., Stephen N. Davis, M.D., Carol Joyce, M.D., Tim Peoples, M.A., Bruce A. Perkins, M.D., M.P.H., John B. Welsh, M.D., Ph.D., Steven M. Willi, M.D., and Michael A. Wood, M.D., for the STAR 3 Study Group*

STAR 3 - multicenter, randomized, controlled trial

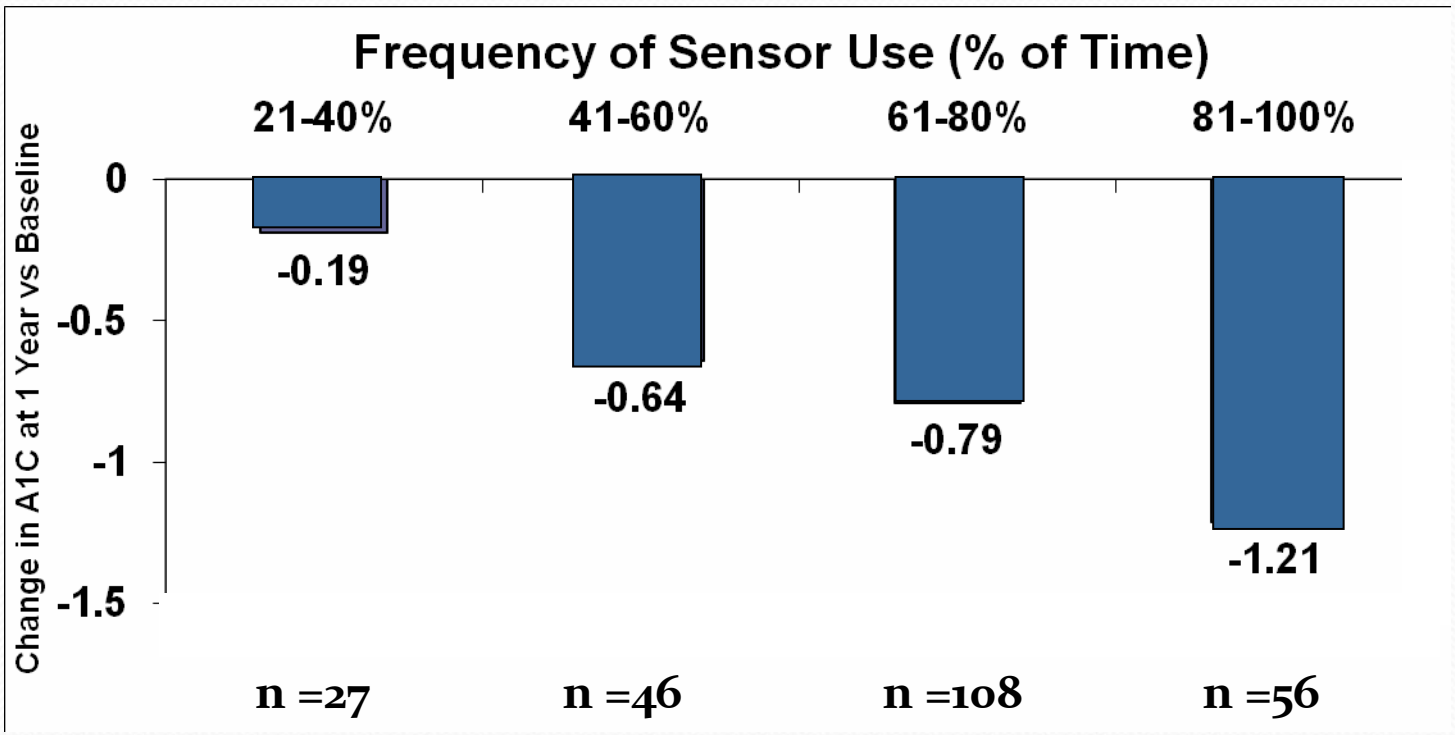
Results Over Time: Adults ≥ 19 years



Values are means ± SE. Comparisons between SAP group and MDI group are significant for each time period (P<0.001).

A1C Reduction is Correlated with Increased Sensor Use

Patients who used sensors ≥81% of the time reduced their mean A1C by 1.2% at 1 year vs. baseline



Values are the difference between the means ± SE. p=0.003 for association between sensor wear and A1C reduction at 1 year. Only 7 participants had sensor use of 20% or less, with a change in A1C of -0.43 at 1 year vs. baseline.

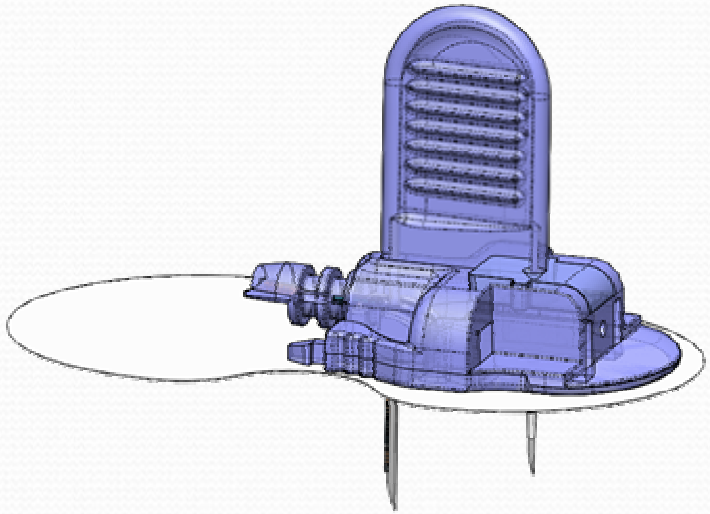
STAR 3 Conclusions

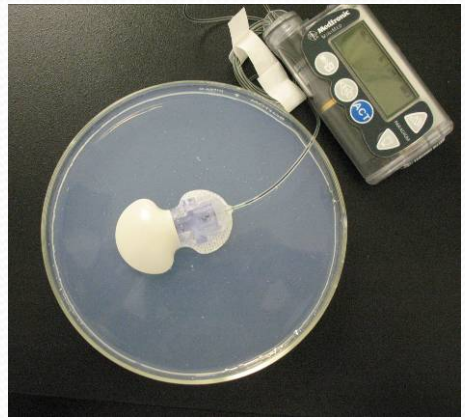
Sensor-augmented insulin pump therapy resulted in…

- A1C (mean) reduction 4x greater than MDI (0.8% v. 0.2%) without an increase in severe hypoglycemia
  - ✓ SAP: from 8.3 % to 7.5%. MDI: from 8.3 % to 8.1%.
- 1.0% A1C (mean) reduction in adults
- Patients wearing sensors ≥81% of the time reduced their mean A1C by 1.2% (reduction from baseline to 1 year)
- Glycemic improvements were seen early (3 months) and were sustained at 1 year

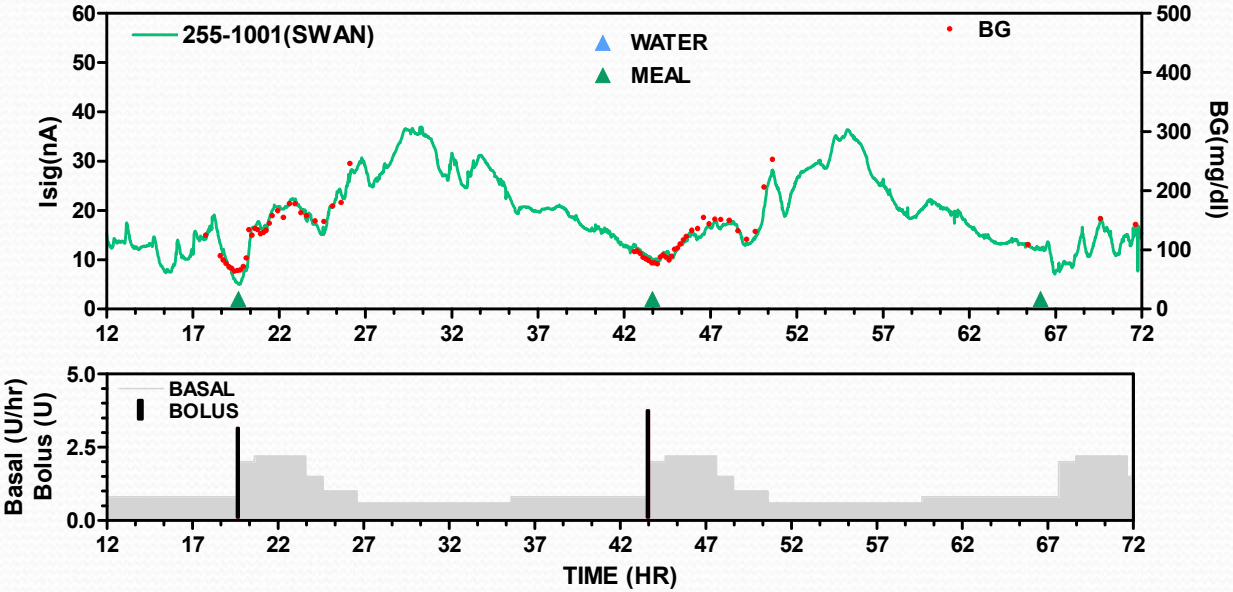
Integrated Infusion Set and Sensor

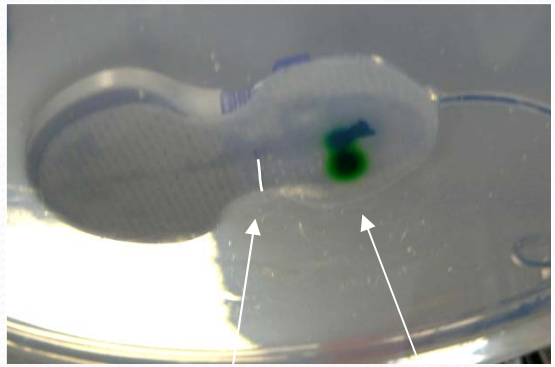
Insertion device





Infusion of insulin in gel shows localization with no insulin reaching sensor





sensor Infusion port

2 GSTs
Translator
916
Meter
Pump
Pump
BT rx: 4/min
BT tx: 1/min
Accelerometer: 10/sec
Remote Monitor 1/min
Carelink Upload 1/day
SMS
GPS
SMS
Remote Cellphone
Network
Network
BlackBerry Storm
ClosedLoop Device
CareLink
Remote Monitoring Station

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