

***Macrovascular Outcomes  
with Antidiabetic Drugs:  
Ongoing Studies***

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# Chronic Consequences of Type 2 DM

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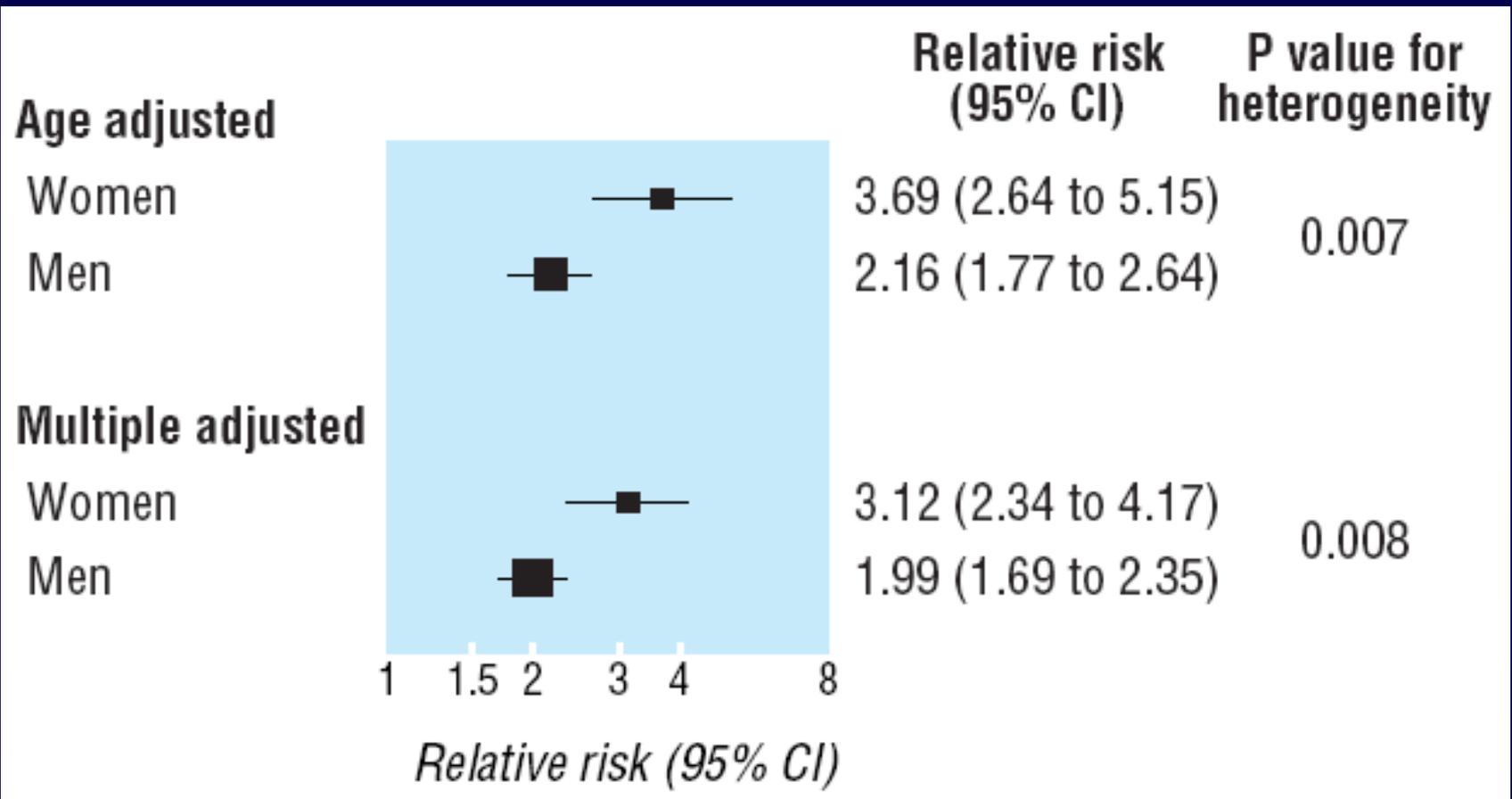
- Eye (cataracts, retina)
- Kidney (CRF, ON)
- Nerve (sensory, motor)
- Foot (pain, ulcer)
- Amputation (BKA)
- Ischemic Heart Disease
- Stroke
- Peripheral Vascular Disease
- Cirrhosis
- Early Death
- Cognitive Decline
- Depression
- Hip Fractures
- Imbalance & Frailty
- Connective Tissue (joint)
- Erectile Dysfunction
- Sexual Dysfunction
- Infertility/PCOS

# Outline

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- **What is the relationship between diabetes & CVD?**
- What is the relationship between glycemia & CVD in people with/without diabetes?
- Does glucose lowering reduce CVD outcomes?
- Do glucose-lowering drugs reduce CVD outcomes?

# Risk of Fatal CHD with Diabetes



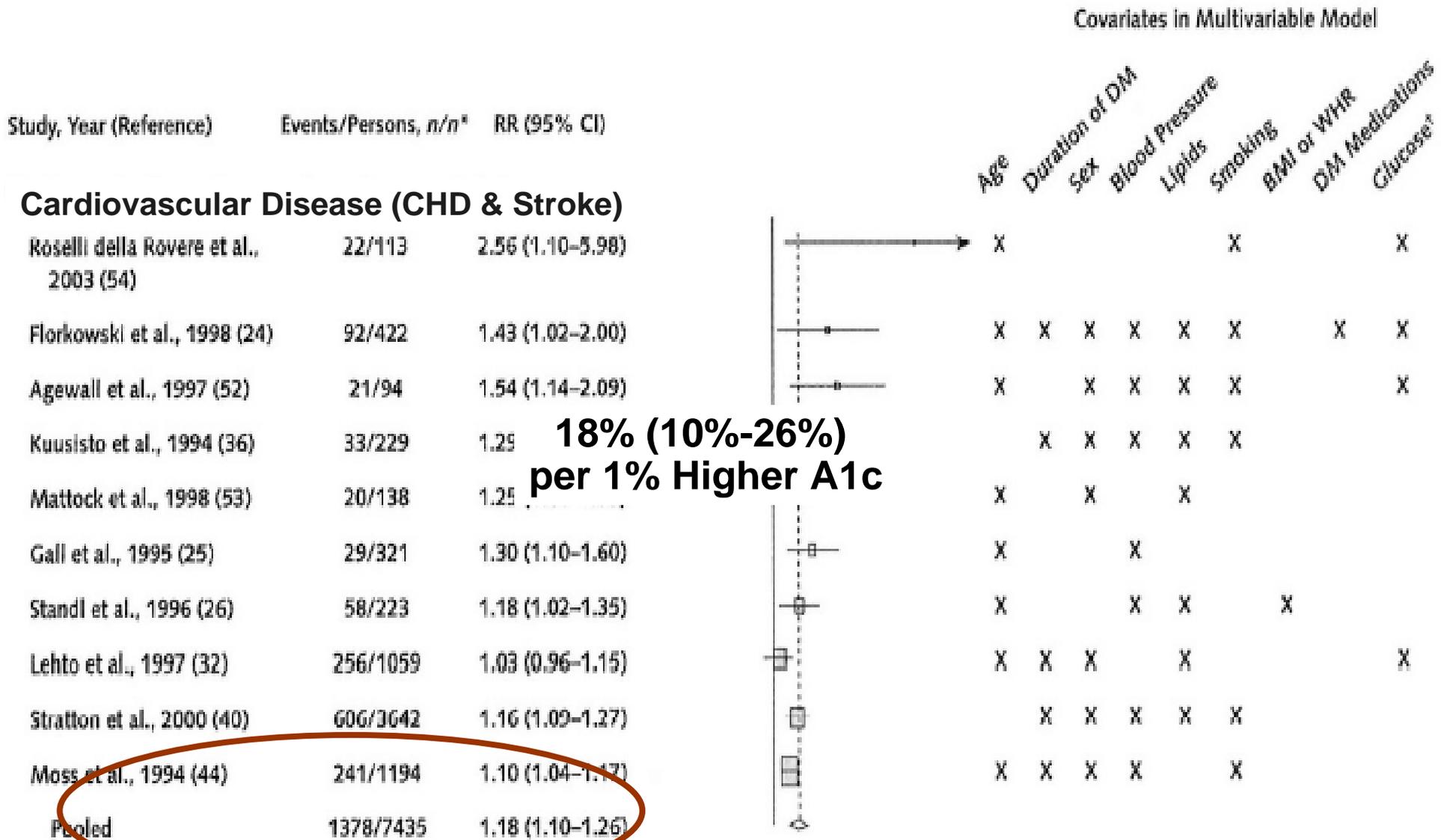
# Outline

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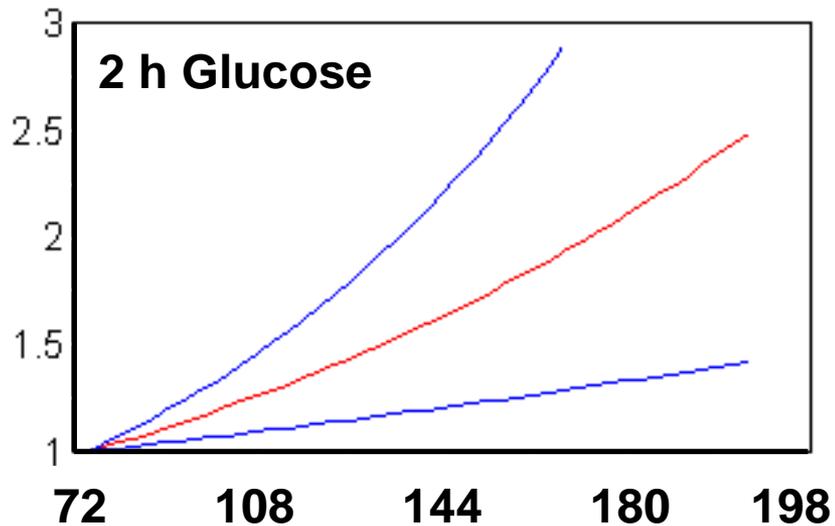
- What is the relationship between diabetes & CVD?
- **What is the relationship between glycemia & CVD in people with/without diabetes?**
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# Meta-Analysis: A1c & CV Risk- DM

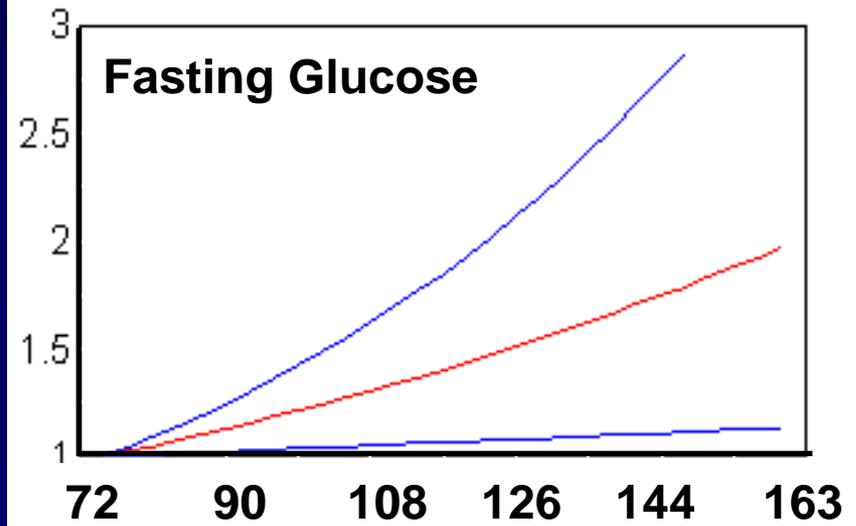
Type 2 DM Studies: Selvin et al. Ann Int Med 2004: 421



# G & CV Events: Meta-Regression



@ 2 hr G = 140.....  
RR=1.58 (1.19-2.10)

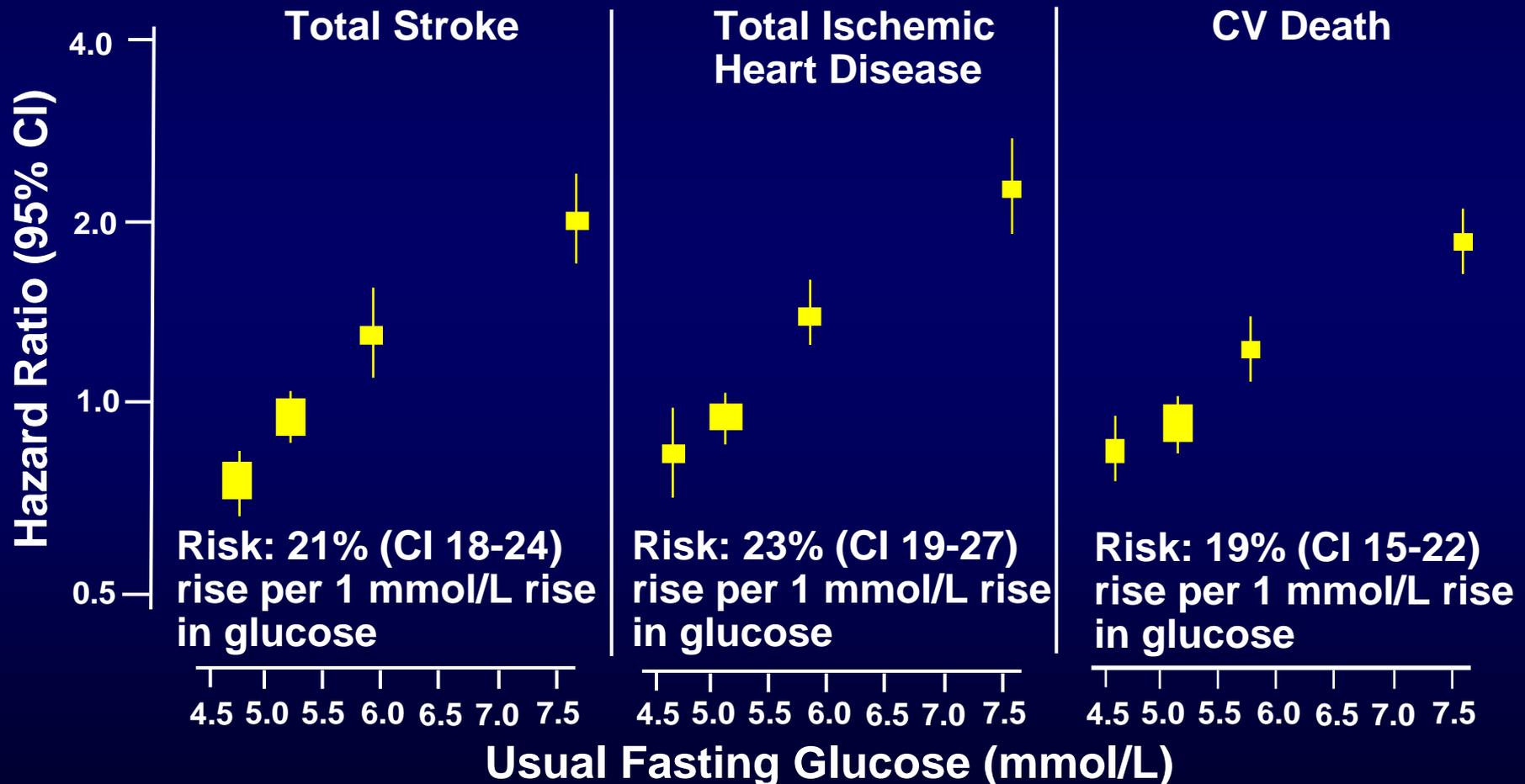


@ Fasting G = 110.....  
RR=1.33 (1.06-1.67)

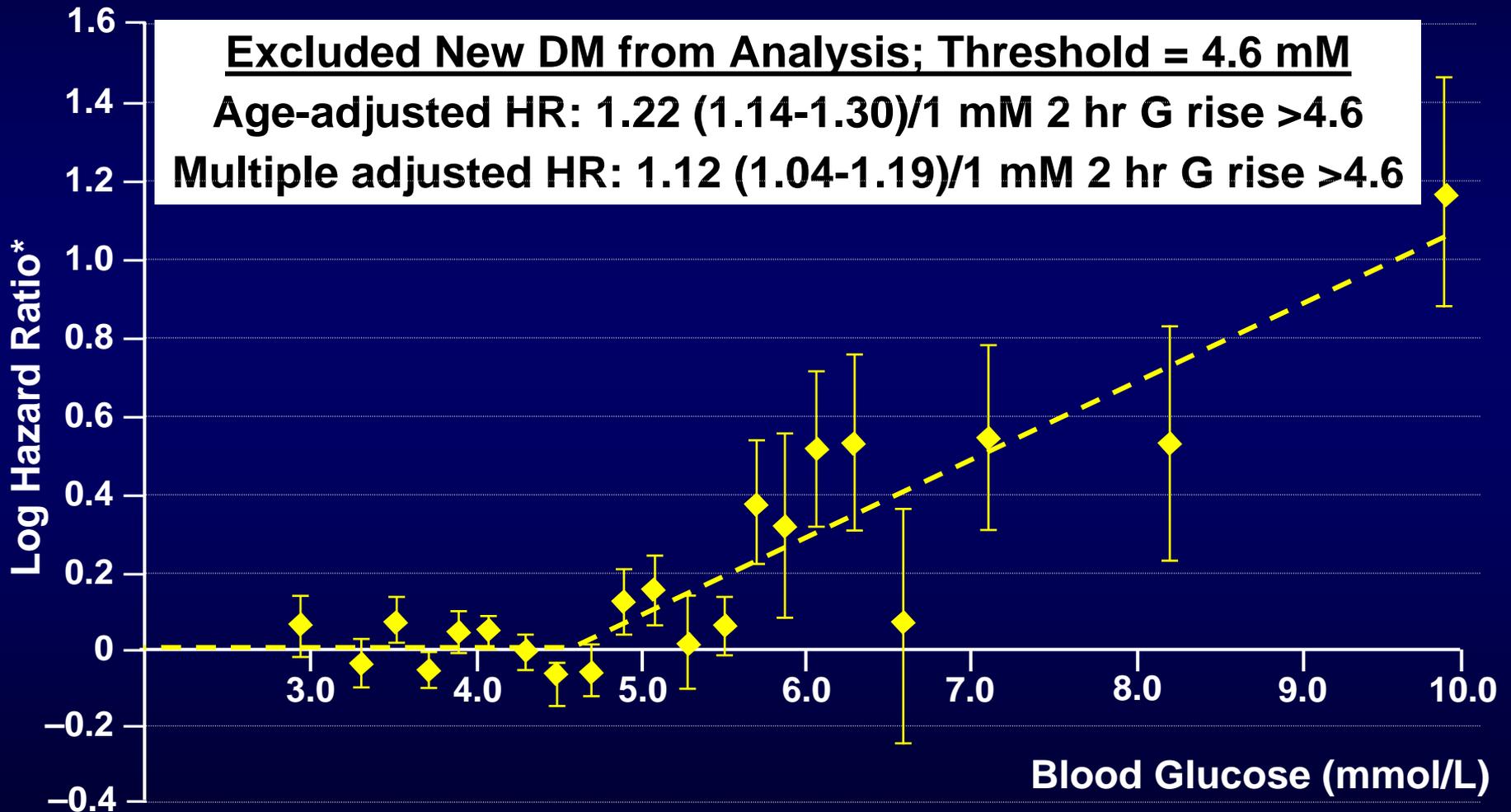
After remove any DM:  $P = 0.0006$  for 2 h G  
 $P = 0.06$  for FPG

# Usual Fasting Glucose vs. CVD

Sex & Study Stratified; Age-adjusted

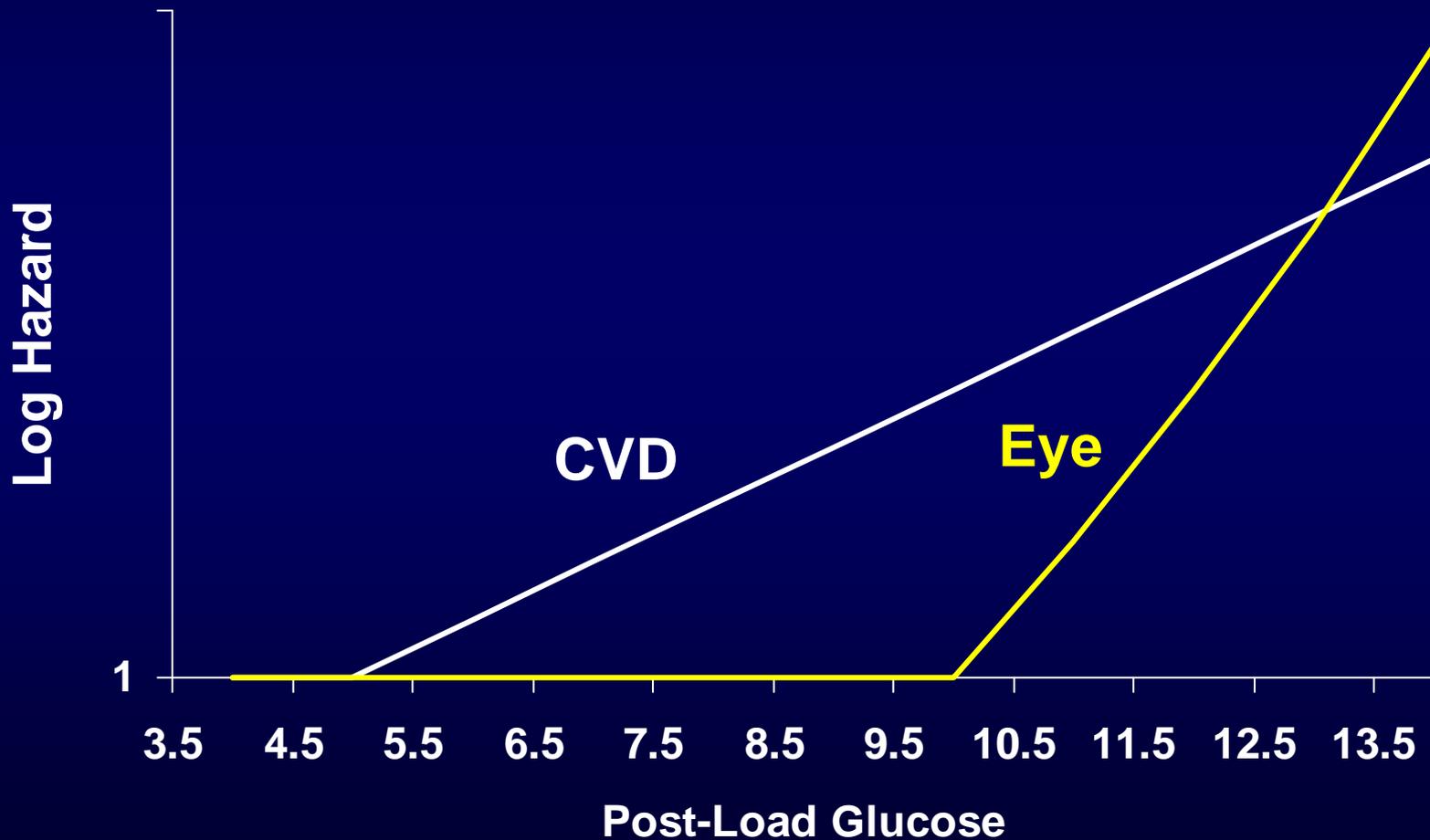


# 2-hr Post 50g Blood G vs. CHD Death



# Cartoon: G & Risk of Problems

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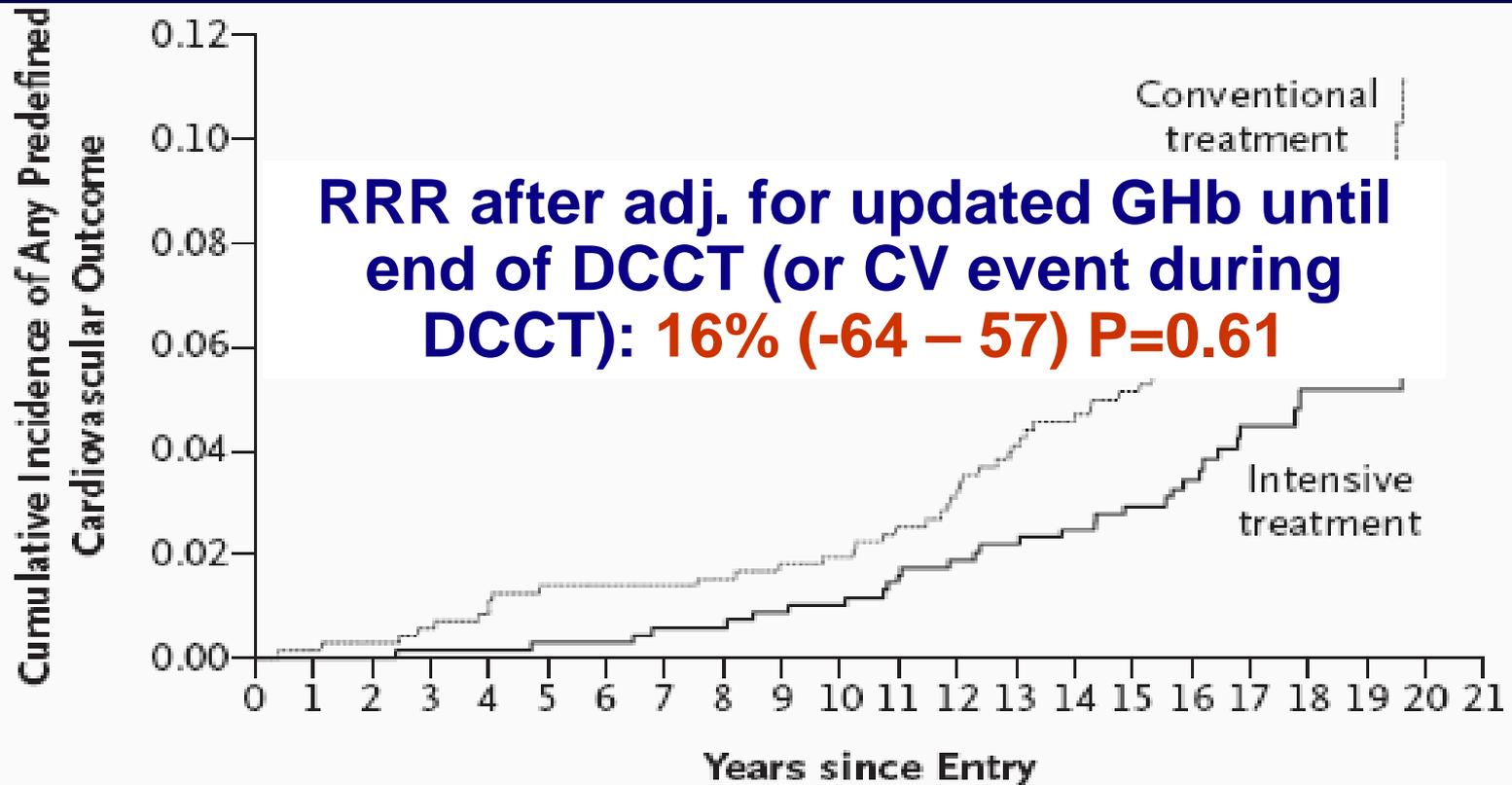
# Outline

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# Intensive Insulin & CVD: Type 1 DM

DCCT/EDIC NEJM 2005;353:2643

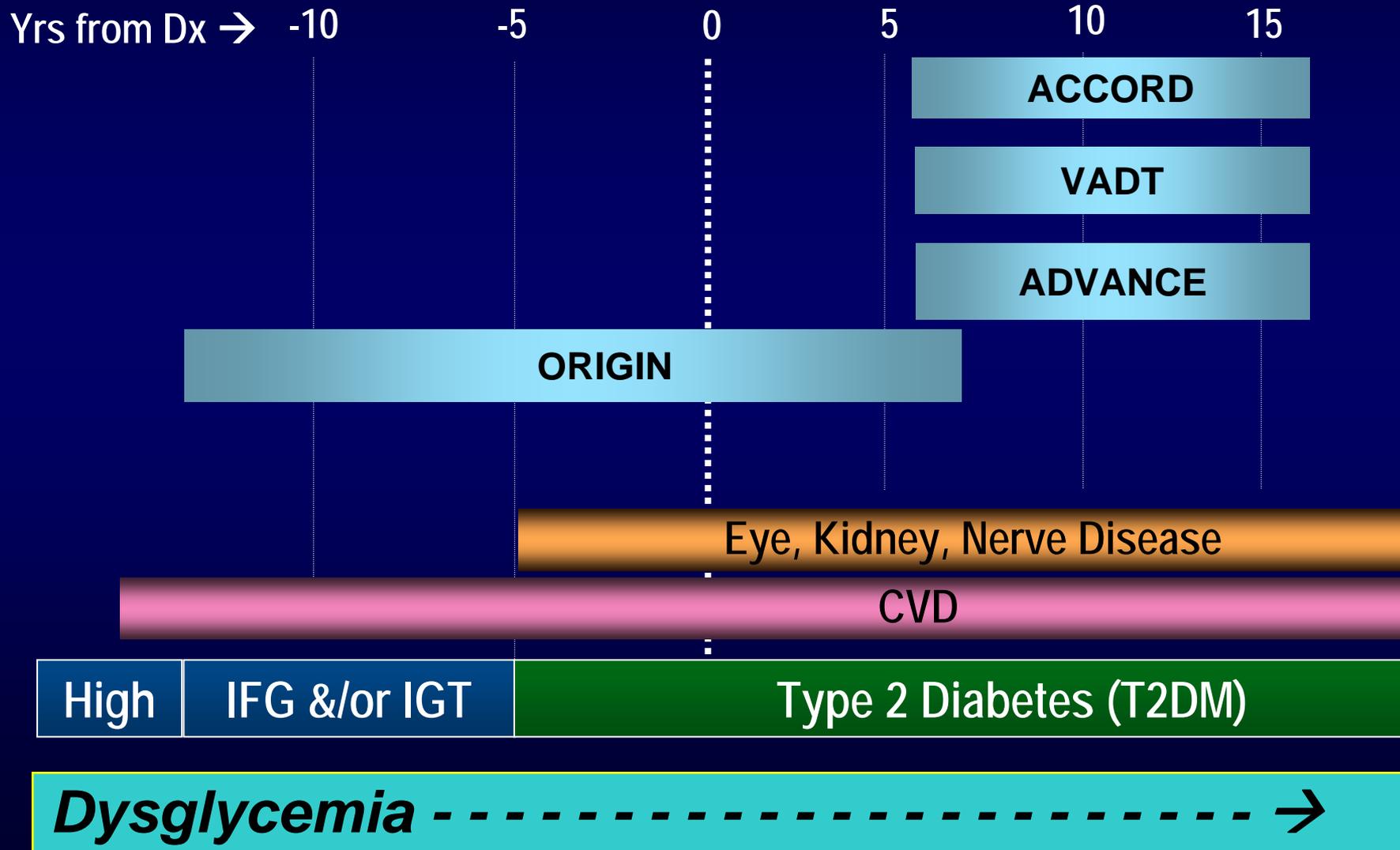


## No. at Risk

Intensive treatment	705	683	629	113
Conventional treatment	714	688	618	92

# G Lowering to Prevent CVD

## Trials in People with Dysglycemia



# ACCORD Question & Participants

## ▶ Research Question:

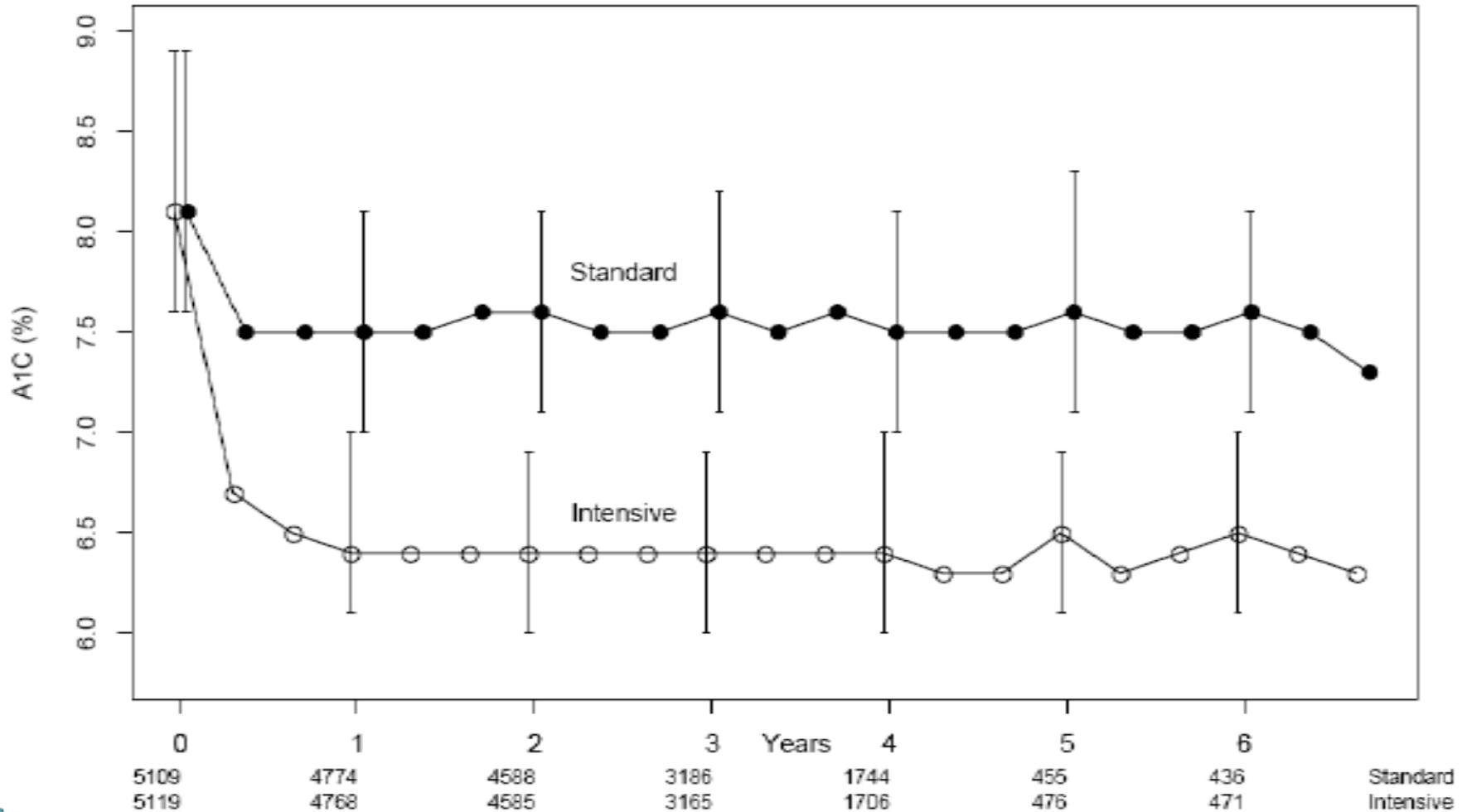
In middle aged or older adults with type 2 DM at high risk for a CVD event because of existing CVD or additional CVD risk factors, does a therapeutic strategy that targets A1C <6.0% reduce the rate of CVD events more than a strategy that targets A1C 7.0% to 7.9%?

## ▶ Participant baseline characteristics:

- Age: average 62 years
- Known DM duration: average 10 years
- Existing CVD: in 35%
- BMI: average 32
- A1C: mean 8.3%; median 8.1%
- On insulin therapy: 35%

NEJM 2008;358:2545

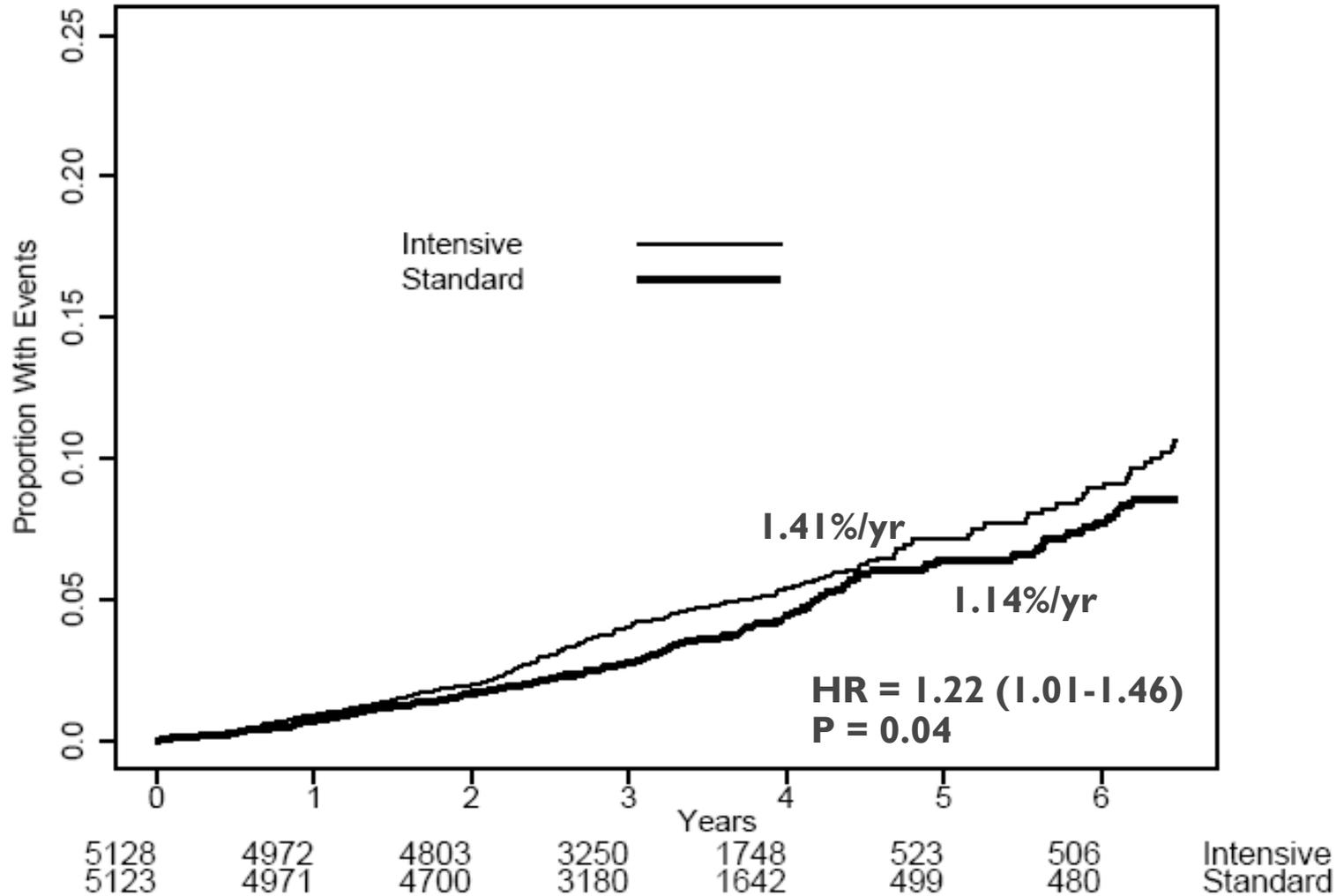
# Median A1C and Interquartile Ranges



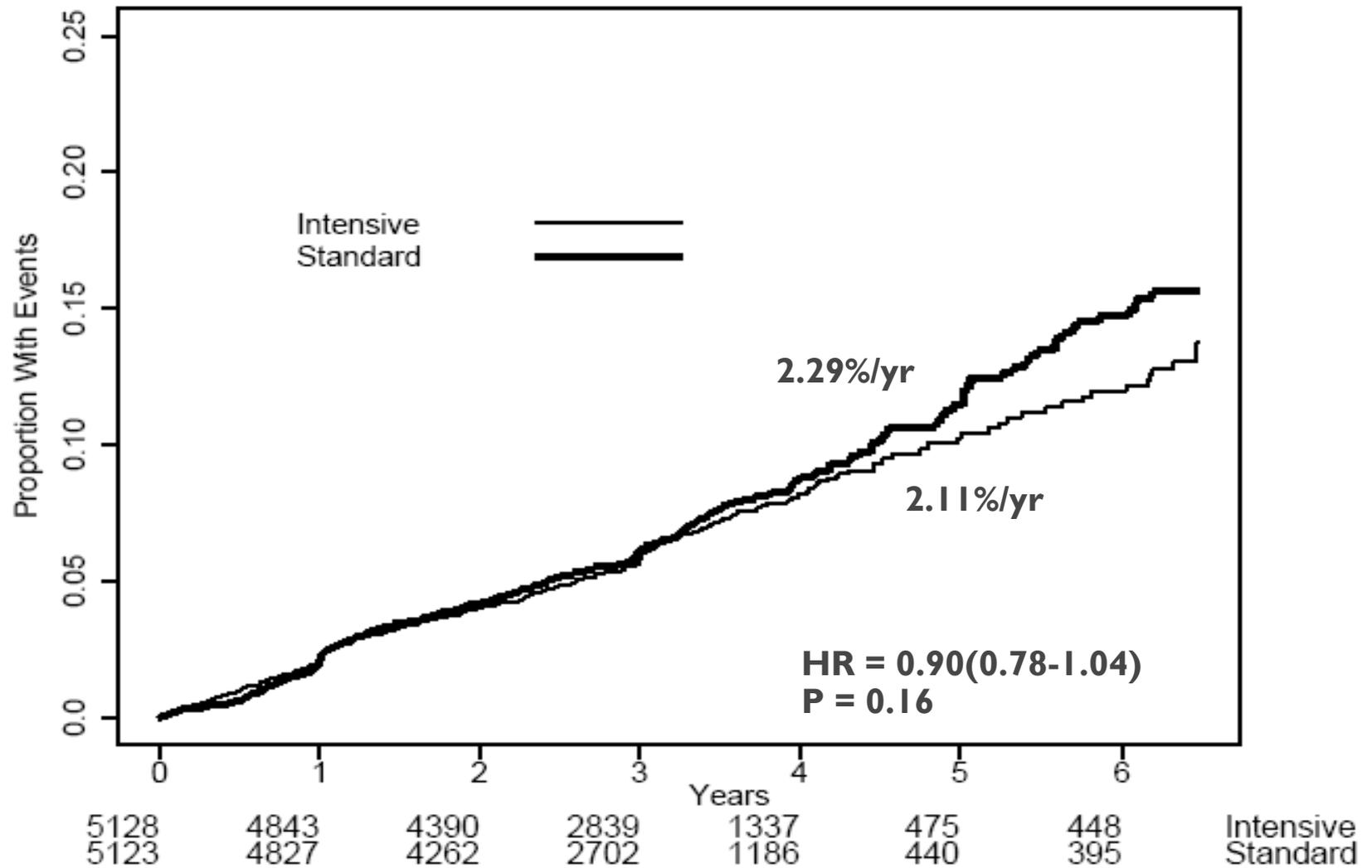
# Primary & Secondary Outcomes

	<b>Intensive N (%)</b>	<b>Standard N (%)</b>	<b>HR (95% CI)</b>	<b>P</b>
Primary	352 (6.86)	371 (7.23)	0.90 (0.78-1.04)	0.16
Secondary				
Mortality	257 (5.01)	203 (3.96)	1.22 (1.01-1.46)	0.04
Nonfatal MI	186 (3.63)	235 (4.59)	0.76 (0.62-0.92)	0.004
Nonfatal Stroke	67 (1.31)	61 (1.19)	1.06 (0.75-1.50)	0.74
CVD Death	135 (2.63)	94 (1.83)	1.35 (1.04-1.76)	0.02
CHF	152 (2.96)	124 (2.42)	1.18 (0.93-1.49)	0.17

# All Cause Mortality



# Primary Outcome



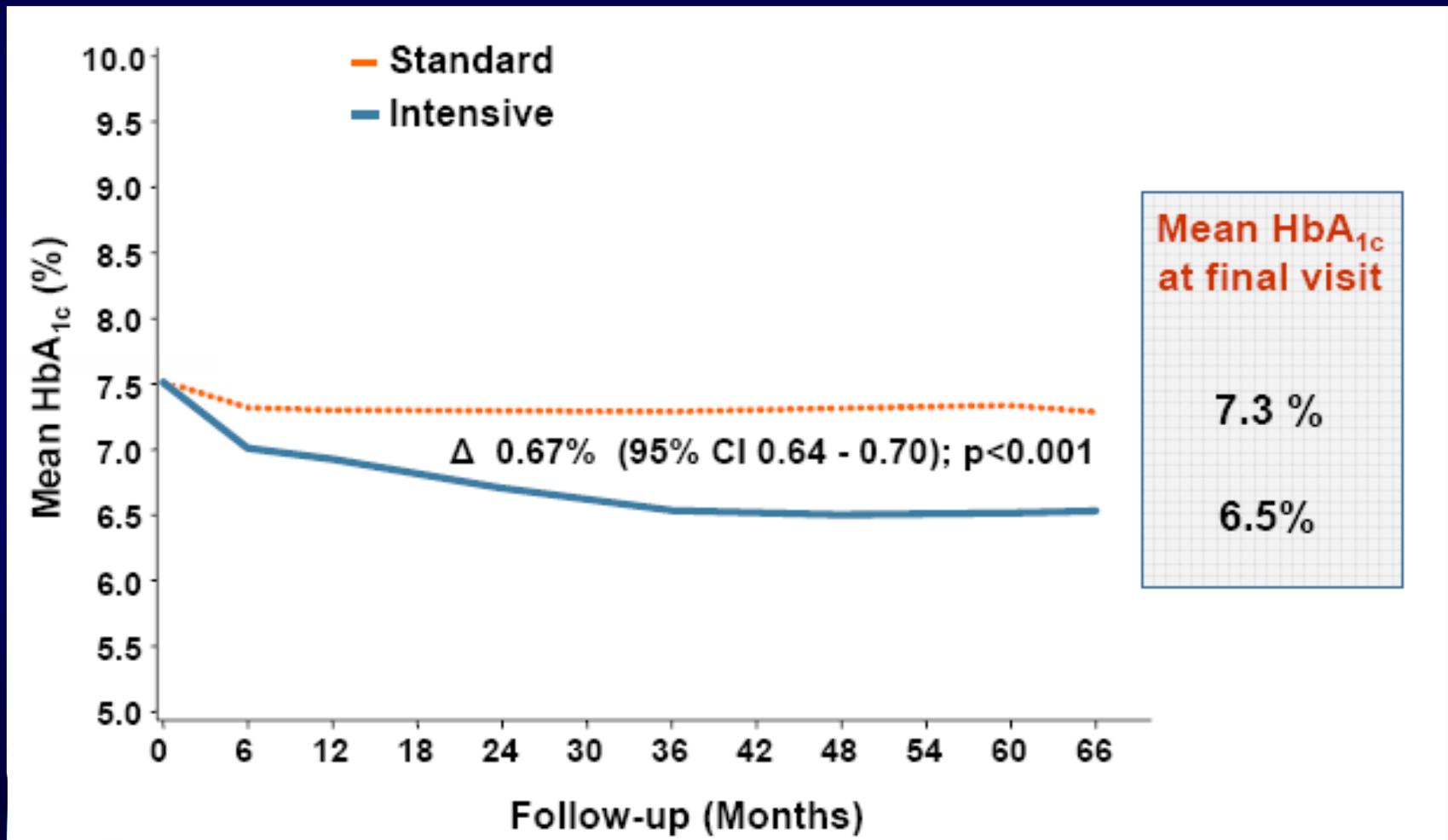
# ADVANCE RCT – Glycemic Question

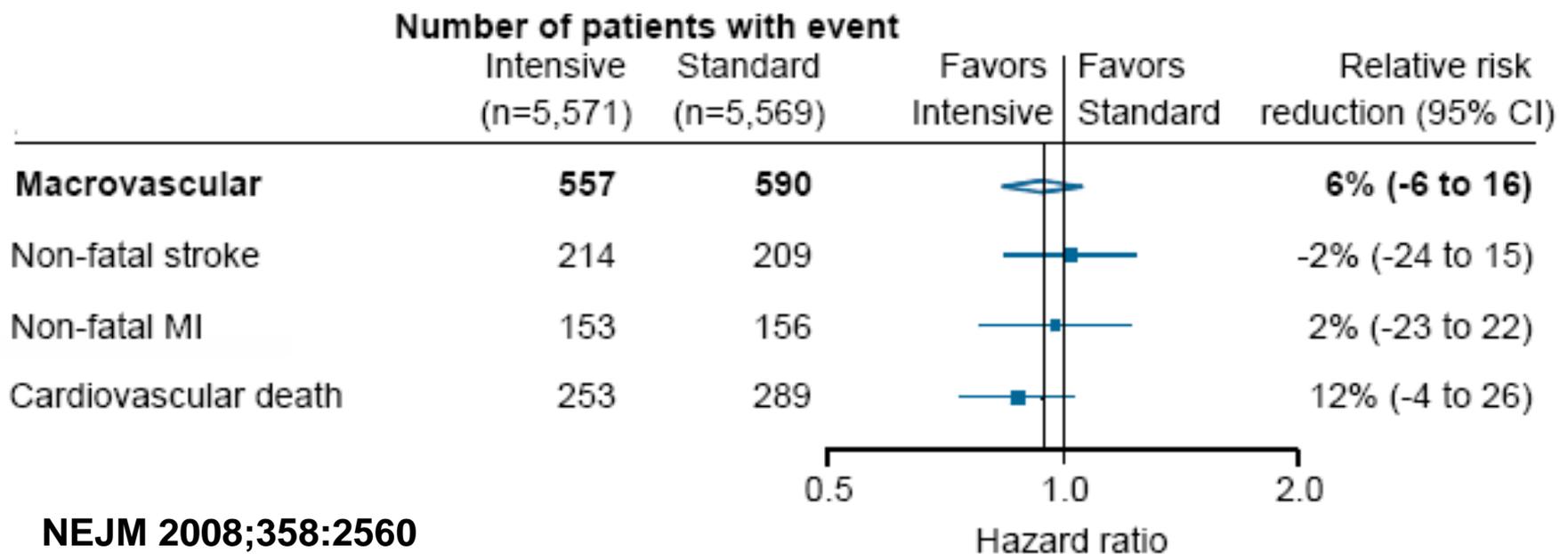
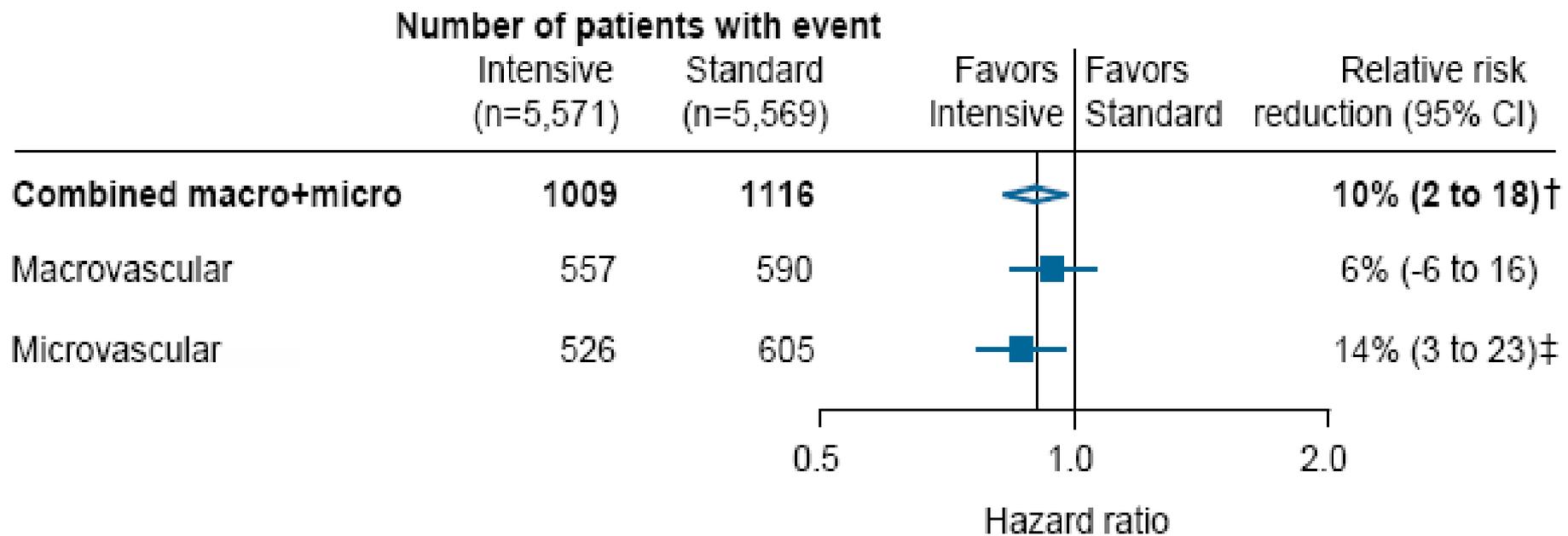
Action in Diabetes and Vascular Disease

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- **Participants**  
N = 11,140; Type 2 DM
- **Eligibility**  
Age  $\geq$  55; DM Dx after age 30; High CV Risk
- **Intervention**  
G Question: Gliclazide based glucose lowering vs. Standard Care; Added Rx  $\rightarrow$  A1c  $\leq$  6.5%
- **Primary Outcome**  
Micro or CVD events
- **Power Issues**  
F/U – 5 yrs; 90% power for 16% RRR

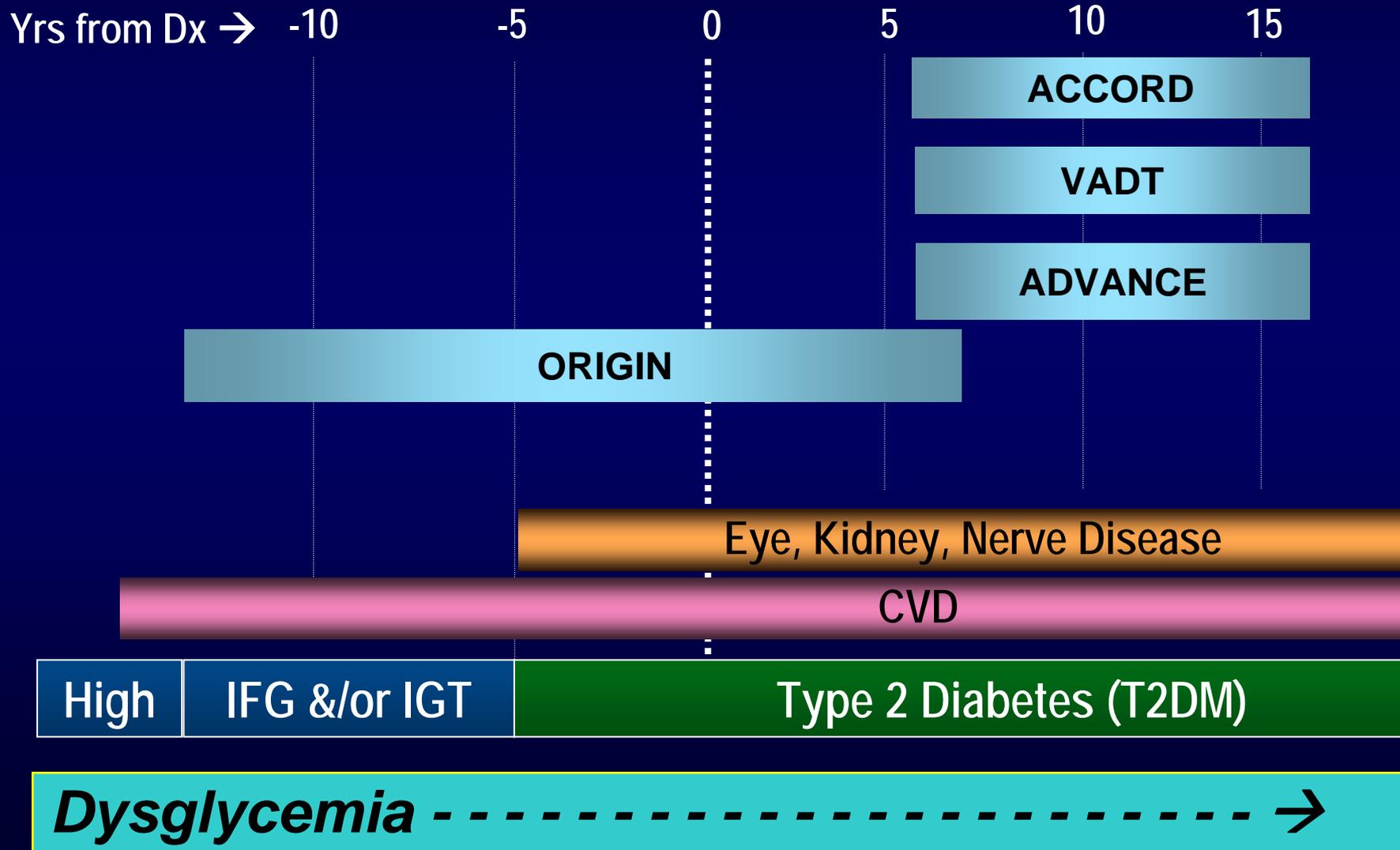
# ADVANCE Results: HbA1c





# G Lowering to Prevent CVD

## Trials in People with Dysglycemia



# Glucose Lowering Trials & CVD

Study	N	Participants	Study Dur'n	A1C/FPG Contrast	Rx Tested
<b>ACCORD</b>	10251	DM X 10 yrs High CV Risk	3.5 yrs	From 8.1% → 6.4% vs. 7.5%	Multiple
<b>ADVANCE</b>	11140	DM X 8 yrs High CV Risk	5 yrs	From 7.2% → 6.4% vs. 7.0%	SU + Multiple
<b>VADT (ADA Presentation)</b>	1791	DM X 11.5 yrs High CV Risk	6.3 yrs	From 9.5% → 6.9% vs. 8.4%	Multiple
<b>ORIGIN (Ongoing)</b>	12612	DM, IFG, IGT	5 yrs	Ongoing Study	Glargine-Mediated FPG ≤ 95

# Glucose Lowering Trials & CVD

Study	N	MI	CVD	Mortality
ACCORD	10251	24% (8, 38)	10% (-4,22)	-22% (-1,-46)
ADVANCE	11140	2% (-23,22)	6% (-6, 16)	7% (-6, 17)
VADT (ADA)	1791	N/A	13% (-4,27)	N/A
ORIGIN (Ongoing)	12612	<i>Ongoing</i>	<i>Ongoing</i>	

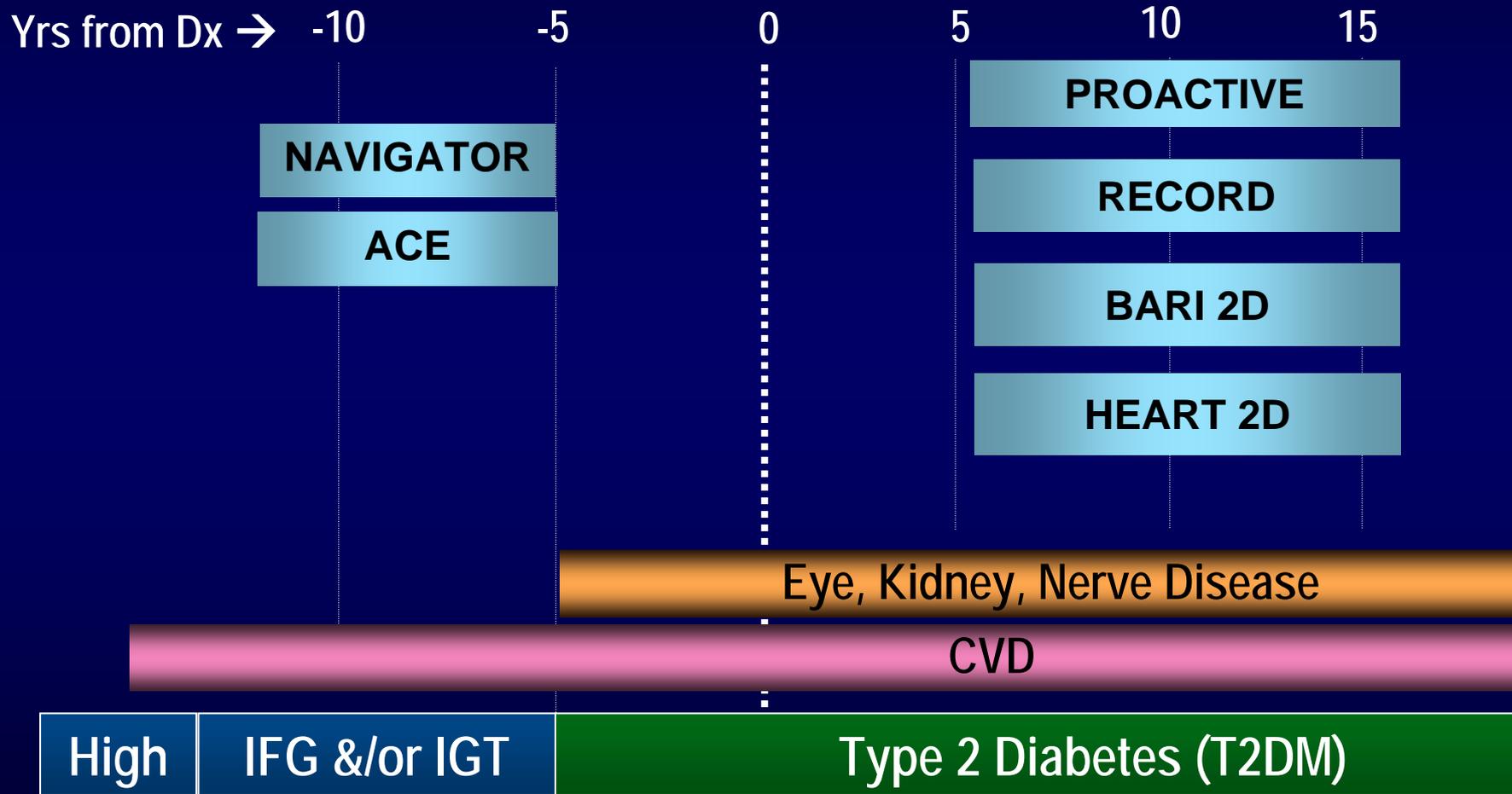
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# G Lowering Drugs to Prevent CVD

## Trials in People with Dysglycemia



**Dysglycemia** - - - - - →

# PROactive RCT

PROspective PioglitAzone Clinical Trial In MacroVascular Events

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- ***Participants***

N = 5238; Type 2 DM X 9.5 yrs; 19 countries; Age=62

- ***Eligibility***

A1c  $\geq$  6.5: 35-75 yrs; high CV risk

No: CHF (NYHA > 2); insulin mono-Rx; ALT>2.5X ULN

- ***Intervention***

Pioglitazone titrated from 15-45 mg over 3 mo. vs. placebo

- ***Primary Outcome***

Death, Non-fatal MI, ACS, revascularization, stroke, leg amputation (above the ankle) or revascularisation

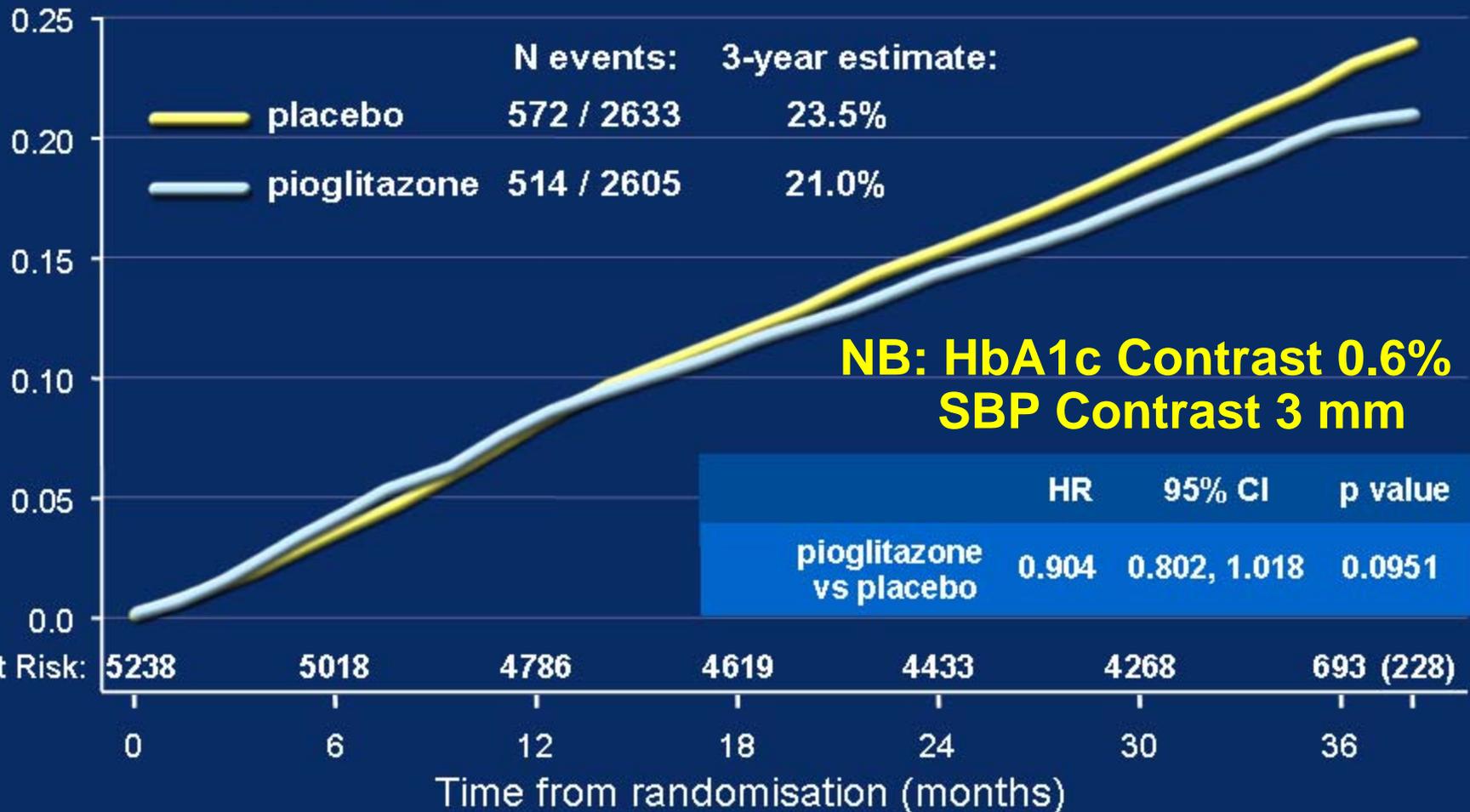
- ***Follow-up & Power***

2.9 years; 90% power for 20% RRR

**Diabetes Care 2004;27:1647**

# Time to Primary Composite Endpoint

Kaplan-Meier event rate



# Interim Results of RECORD

Rosiglitazone Evaluated for Cardiac Outcomes & Regulation of Glycemia in Diabetes

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- ▶ **Question:** Is rosi + either MET or SU non-inferior (upper CI of HR  $\leq 1.2$ ) to SU + MET re CVD?
- ▶ **Design:** Open label, blinded outcome ascertainment  
**No difference in glucose levels by group**
- ▶ **Pts:** N=4447; HbA1c 7-9% on max MET or SU
- ▶ **Contrast:** Rosi + MET/SU, vs. SU + MET; HbA1c target for both groups was the same (< 7%)
- ▶ **Outcome:** CV hosp (includes CHF) or CV death
- ▶ **F/U Plan:** Median of 6 yrs: **UNPLANNED PUB 3.75 yrs**
- ▶ **Power:** 99% to detect noninferiority assuming a control event rate 11%/yr (3%/yr CV death & 8%/yr CV hospitalization)

# Interim Results of RECORD

Rosiglitazone Evaluated for Cardiac Outcomes & Regulation of Glycemia in Diabetes

<b>Outcome</b>	<b>Rosi N=2220</b>	<b>Met/SU N=2227</b>	<b>HR (CI)</b>	<b>P</b>
<b><i>CV Hosp/CV Dth</i></b>	217 (9.8)	202 (9.1)	1.08 (0.89-1.31)	0.43
<b>CV Death</b>	29 (1.3)	35 (1.6)	0.83 (0.51-1.36)	0.46
<b>Any Death</b>	74 (3.3)	80 (3.6)	0.93 (0.67-1.27)	0.63
<b>Acute MI</b>	43 (1.9)	37 (1.7)	1.16 (0.75-1.81)	0.50
<b>CHF</b>	38 (1.7)	17 (0.76)	2.24 (1.27-3.97)	0.006
<b>MI/Stroke/CV Death</b>	93 (4.2)	96 (4.3)	0.97 (0.73-1.29)	0.83

# Conclusions

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- Diabetes & non-diabetic dysglycemia may be present for decades and are strong risk factors for CVD; a key determinant of this risk is the elevated glucose
- Despite trends, reported trials of intensive glucose lowering **strategies** have not detected CVD benefits in advanced DM
- If there is a benefit in such people it will be modest (15-20%) initially, and require  $\geq 5$  years to clearly emerge
- Trials of antidiabetic agents/strategies need to be **long enough (at least 5 years) and large enough** to allow any beneficial effect to emerge or to establish non-inferiority
- Short trials may miss benefits & only detect adverse effects

# Conclusions

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- Whether glucose lowering (or prevention of its rise) by an antidiabetic agent reduces CVD in people with early diabetes or prediabetes remains unknown & is being tested
- Whether most specific antidiabetic agents reduce CVD or other clinical outcomes remains unknown and needs testing
- If such an agent is effective it may either be due to the agent, and/or its effects on glucose, BP, etc....
- The only antidiabetic agent shown to reduce CVD in a 10 year trial is metformin (not replicated)

# Final Conclusions

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- Diabetes increases the risk of many serious diseases; **CVD is not the only clinically important outcome**
- Antidiabetic agents that will make a difference are those that will be proven to reduce clinically important outcomes, and not just glucose levels
- These outcomes may include CVD but do not necessarily have to include CVD

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