

# *The Effect of Glucose Lowering Therapies on CV Outcomes*

## *The Evidence*

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# Disclosures

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- *Advisory Panel Honoraria: Sanofi, Eli Lilly, Novo Nordisk, BI, AZ/BMS, GSK*
- *Consultant Honoraria: Sanofi, Eli Lilly, Roche*
- *Speaker Honoraria: Sanofi*
- *Research Support: (to PHRI) Sanofi, Eli Lilly*

*The Effect of Glucose Lowering  
Therapies on CV Outcomes*

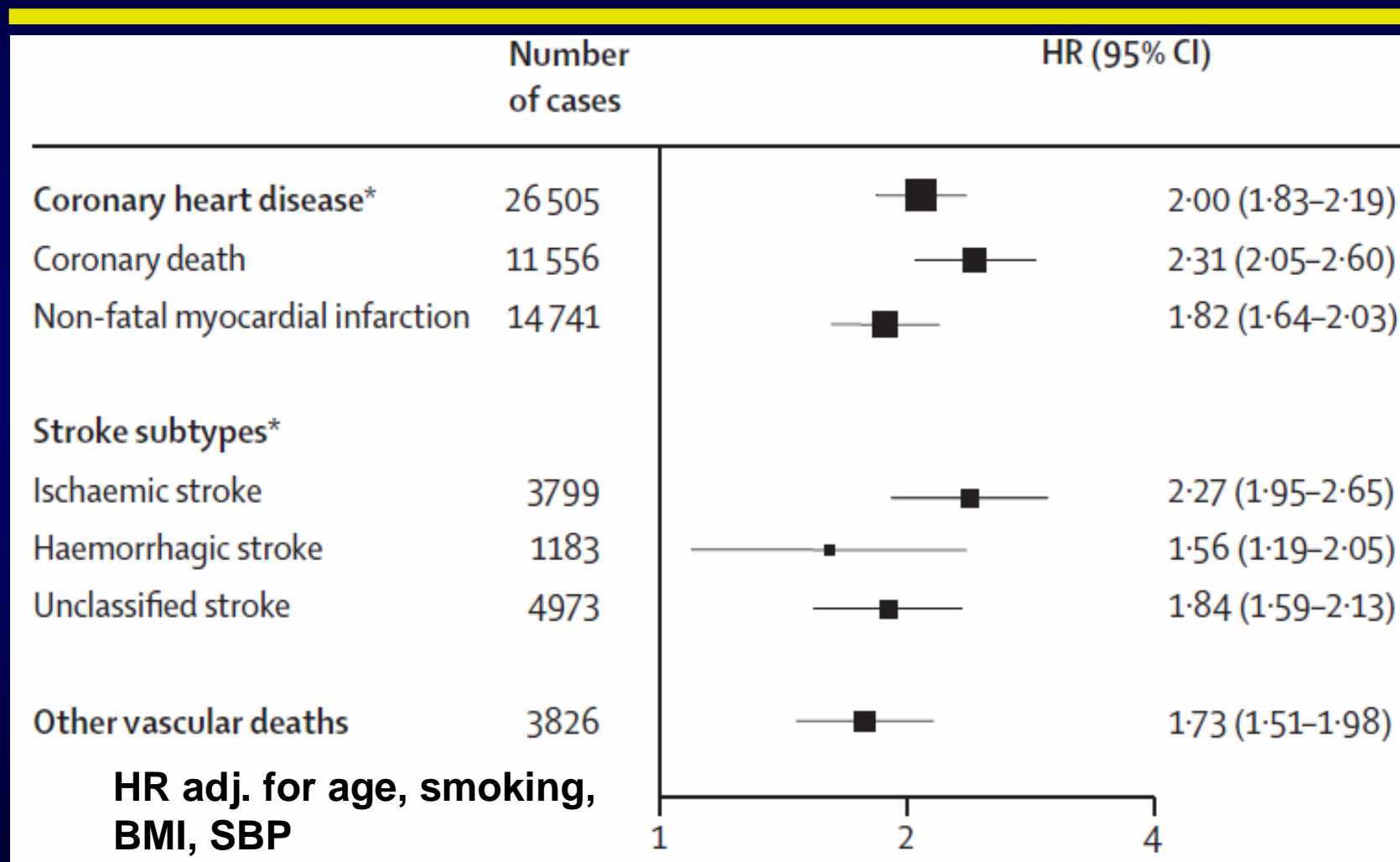
*The Evidence*

# Outline

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- Dysglycemia & Cardiovascular Outcomes
- The Best Evidence re:
  - *Glucose Lowering Intensity*
  - *Glucose Lowering Approaches*
- Summary

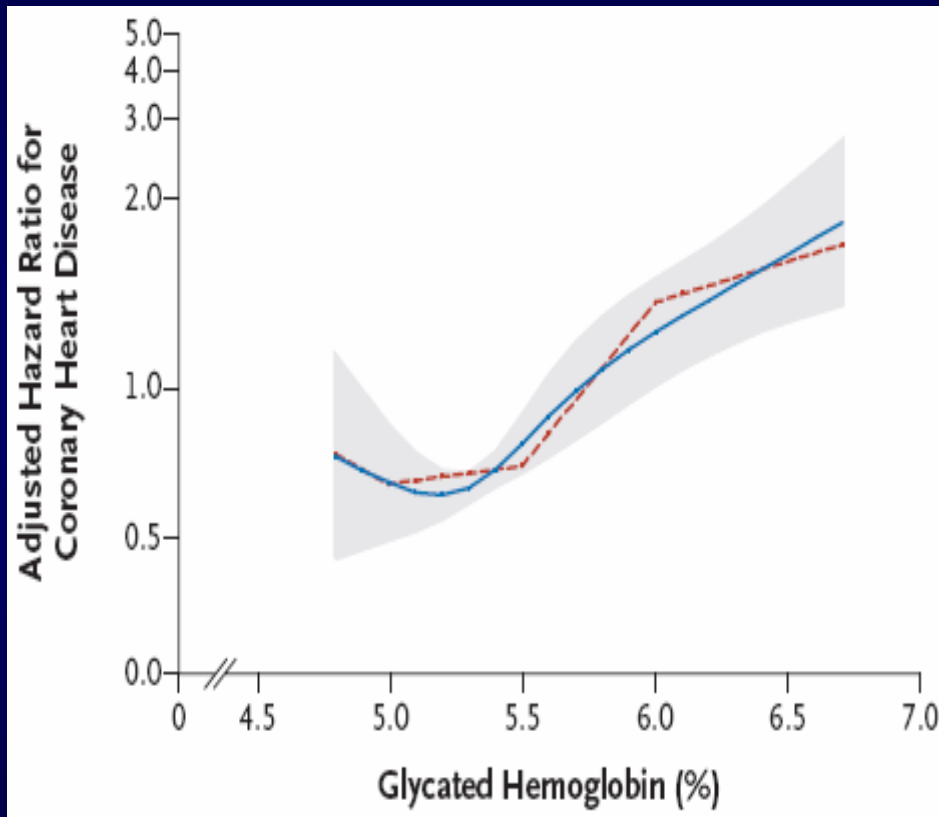
# DM & the Risk of CV Outcomes



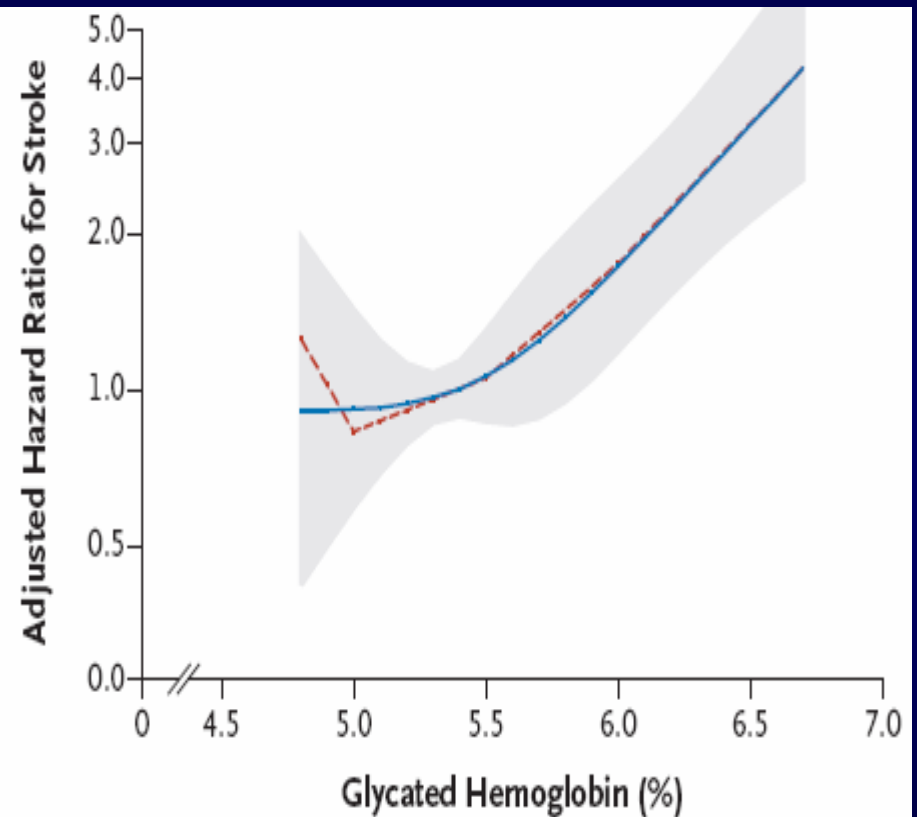
Lancet 2010; 2215 (102 prospective studies, 700K people, 8.5M p-years f/u)

# A1c & CV Outcomes: General Pop'n

## No History of DM or CVD



**HR per 1% higher A1c  
= 1.50 (1.33-1.68)**



**HR per 1% higher A1c  
= 1.55 (1.28-1.88)**

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# Type 2 DM: G Lowering Trials

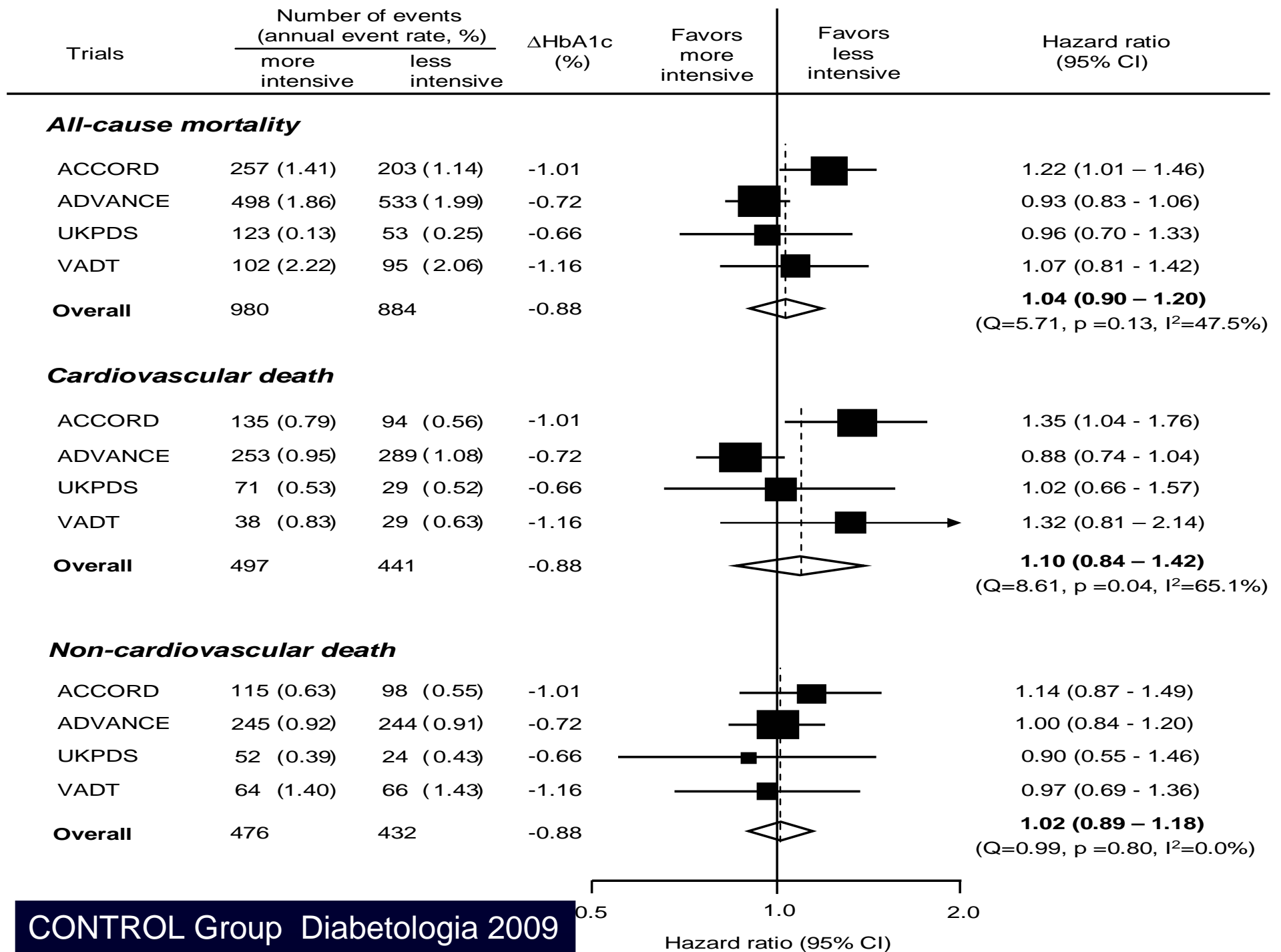
## ACTIVE Rx PHASE

Study	Duration (yrs)	N	Glycemia	
			Target	Achieved
UKPDS	10	3867	FPG < 6 (110)	A1C = 7.0% vs. 7.9%
ACCORD	3.5	10251	A1C < 6.0%	A1C = 6.4% vs. 7.5%
ADVANCE	5	11140	A1C < 6.5%	A1C = 6.5% vs. 7.3%
VADT	6.3	1791	A1C < 6.0%	A1C = 6.9% vs. 8.4%



# Effect of > 4 y of Glucose Lowering on CV Events in Type 2 Diabetes

CVD	Effect	Effect Size	Age (y)	F/U (y)	Evidence
<b>MI</b>	Reduced	0.85 (0.76, 0.94)	53-66	3.5-5.6	Meta-analysis
<b>MACE</b>	Reduced	0.91 (0.84, 0.99)	53-66	3.5-5.6	Meta-analysis
<b>CHF</b>	No Effect	N/A	53-66	3.5-5.6	Meta-analysis
<b>Stroke</b>	No Effect	N/A	53-66	3.5-5.6	Meta-analysis
<b>PAD</b>	No Effect	N/A	53	12	UKPDS
<b>CV Death</b>	No Effect	N/A	53-66	3.5-5.6	Meta-analysis
	Increased	1.29 (1.04, 1.60)	62	5	ACCORD
<b>Death</b>	No Effect	N/A	53-66	3.5-5.6	Meta-analysis
	Reduced	0.87 (0.79, 0.96)	53	17	UKPDS
	Increased	1.19 (1.03, 1.38)	62	5	ACCORD



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# BARI 2D Trial

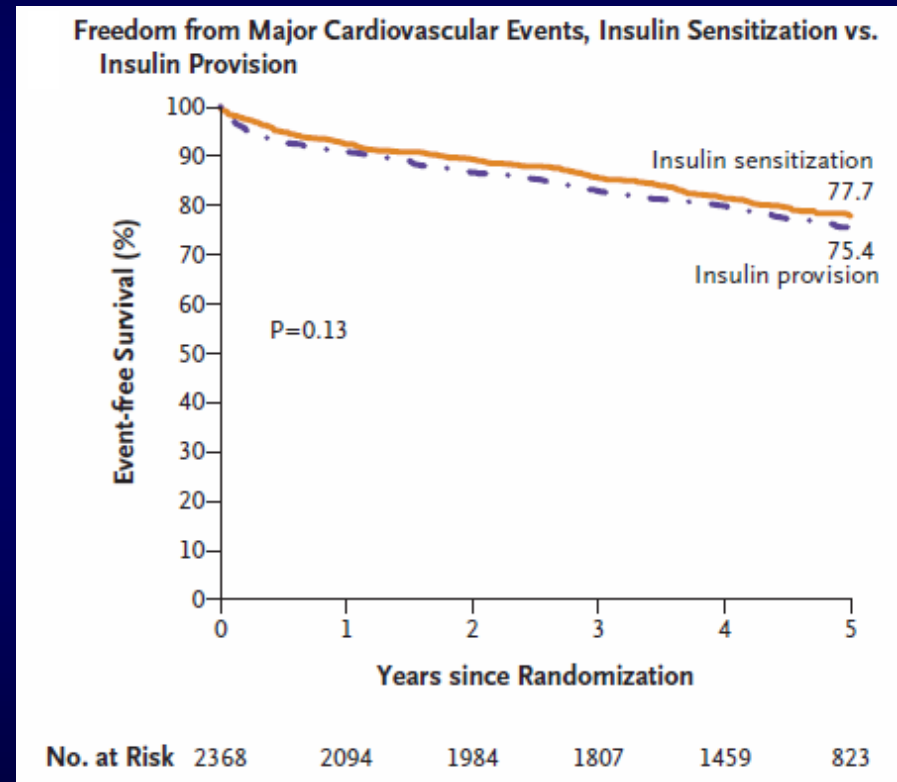
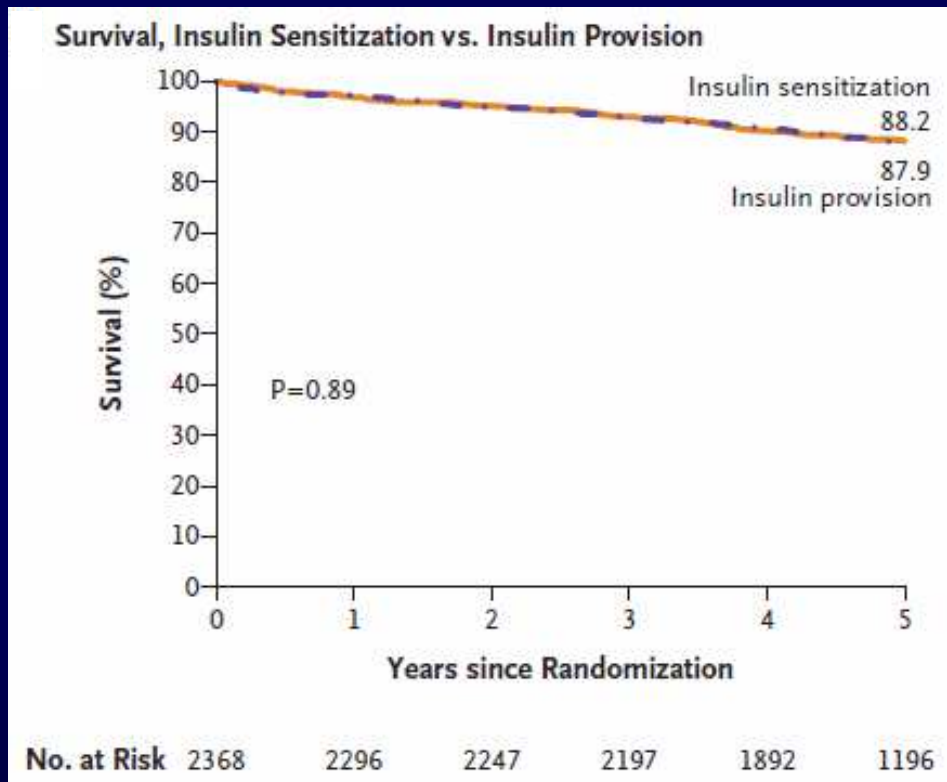
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- **Participants:** N=2368 with type 2 DM (30% female; mean age = 63; median A1C = 7.7%, mean DM duration 10.4 years)

Angiographically proven CAD with symptoms

- **Stratification:** best treated with PCI (1605) or CABG (763)
- **Allocation:** a) insulin sensitization vs. provision  
b) medical Rx vs. revascularization
- **Mean F/U:** 5.3 years

# Combinations of Insulin Sensitizing vs. Insulin Providing Drugs: BARI 2D



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# Glucose Lowering Drugs & Outcomes

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- Sulfonylureas
- Metformin
- Meglitinides
- TZDs
- Insulin
- Acarbose
- GLP-1 analogs
- DPP4 inhibitors
- SGLT-2 inhibitors
- Other drugs
  - Colesavalam
  - Bromocriptine
  - Pramlintide

# Glucose Lowering Drugs & Outcomes

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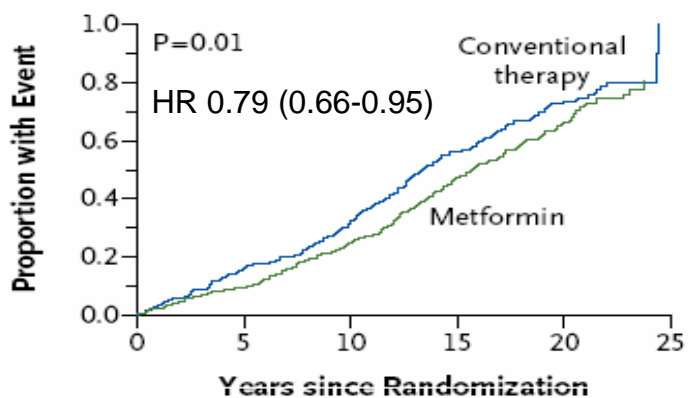
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# Metformin & Outcomes: New T2DM

## UKPDS F/U NEJM 2008;359:1-13

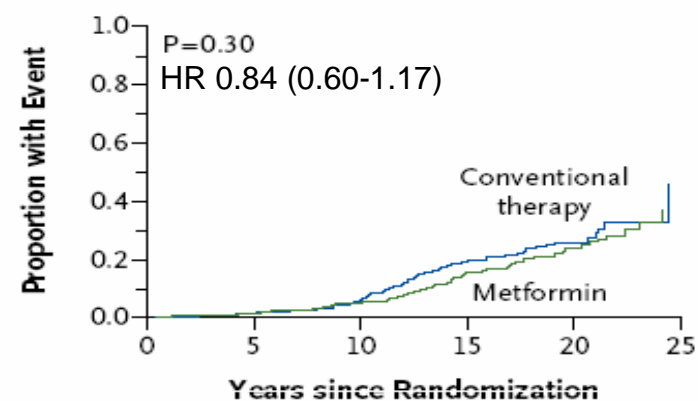
**B Any Diabetes-Related End Point**



**No. at Risk**

Conventional therapy	411	333	255	132	45	2
Metformin	342	300	236	144	62	7

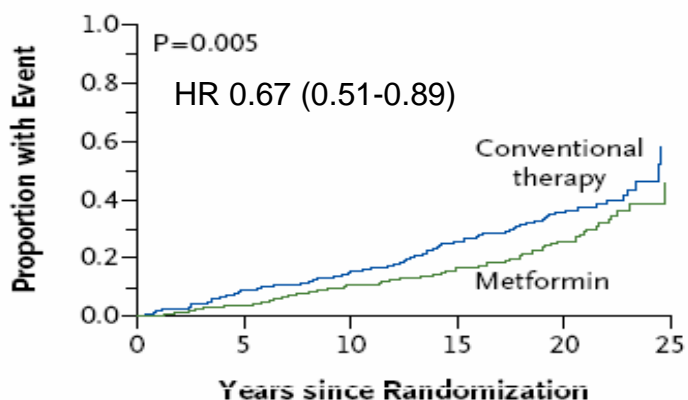
**F Microvascular Disease**



**No. at Risk**

Conventional therapy	411	377	316	186	72	2
Metformin	342	319	278	197	92	16

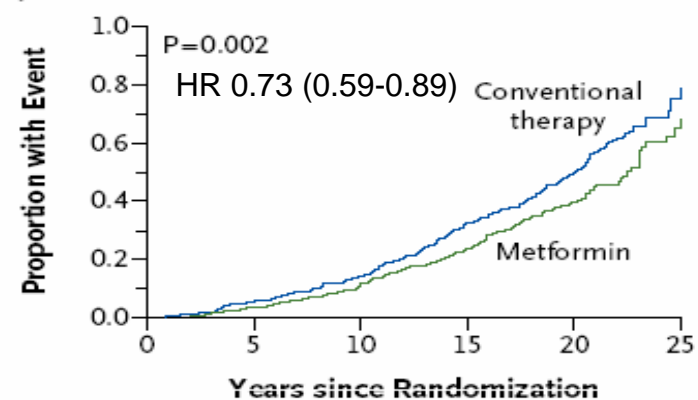
**D Myocardial Infarction**



**No. at Risk**

Conventional therapy	411	360	311	213	95	4
Metformin	342	317	274	214	106	16

**H Death from Any Cause**



**No. at Risk**

Conventional therapy	411	387	345	246	116	7
Metformin	342	328	296	239	124	11

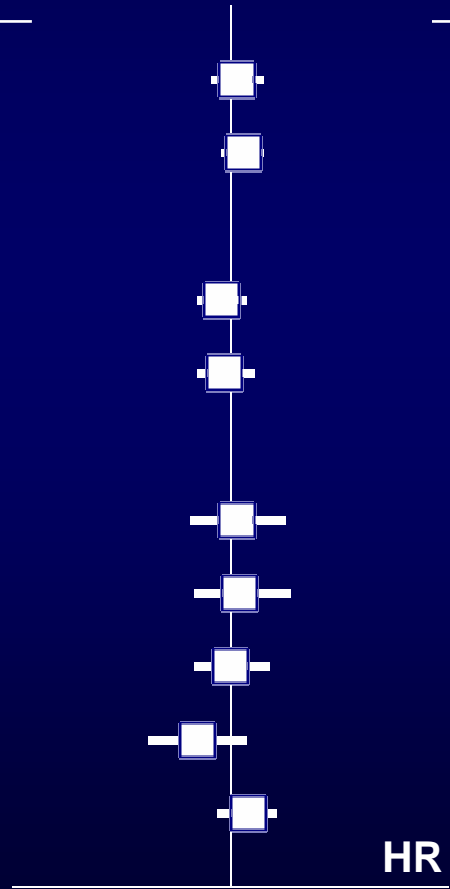
# Glucose Lowering Drugs & Outcomes

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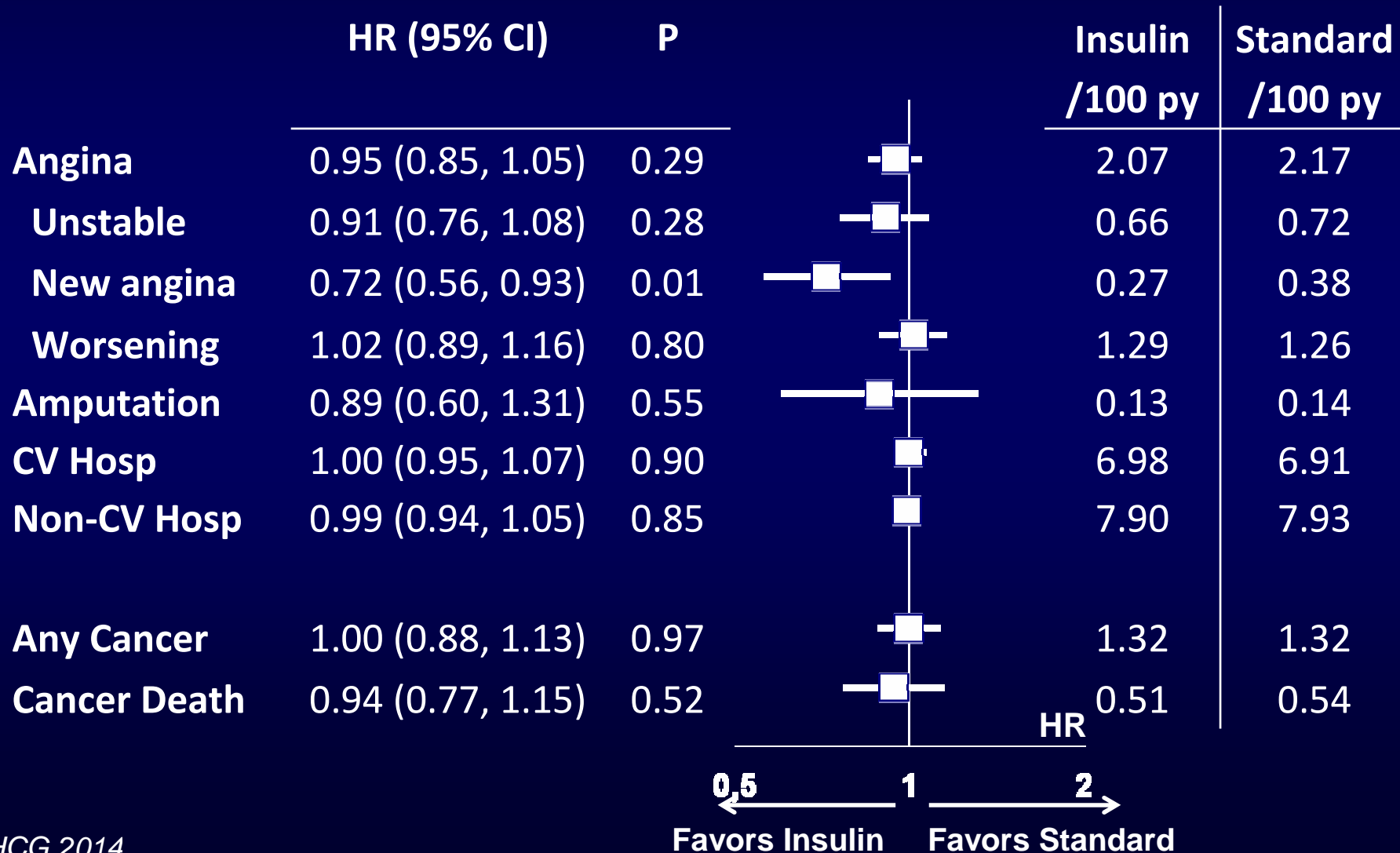
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# ORIGIN: Primary & Secondary Outcomes & their Components

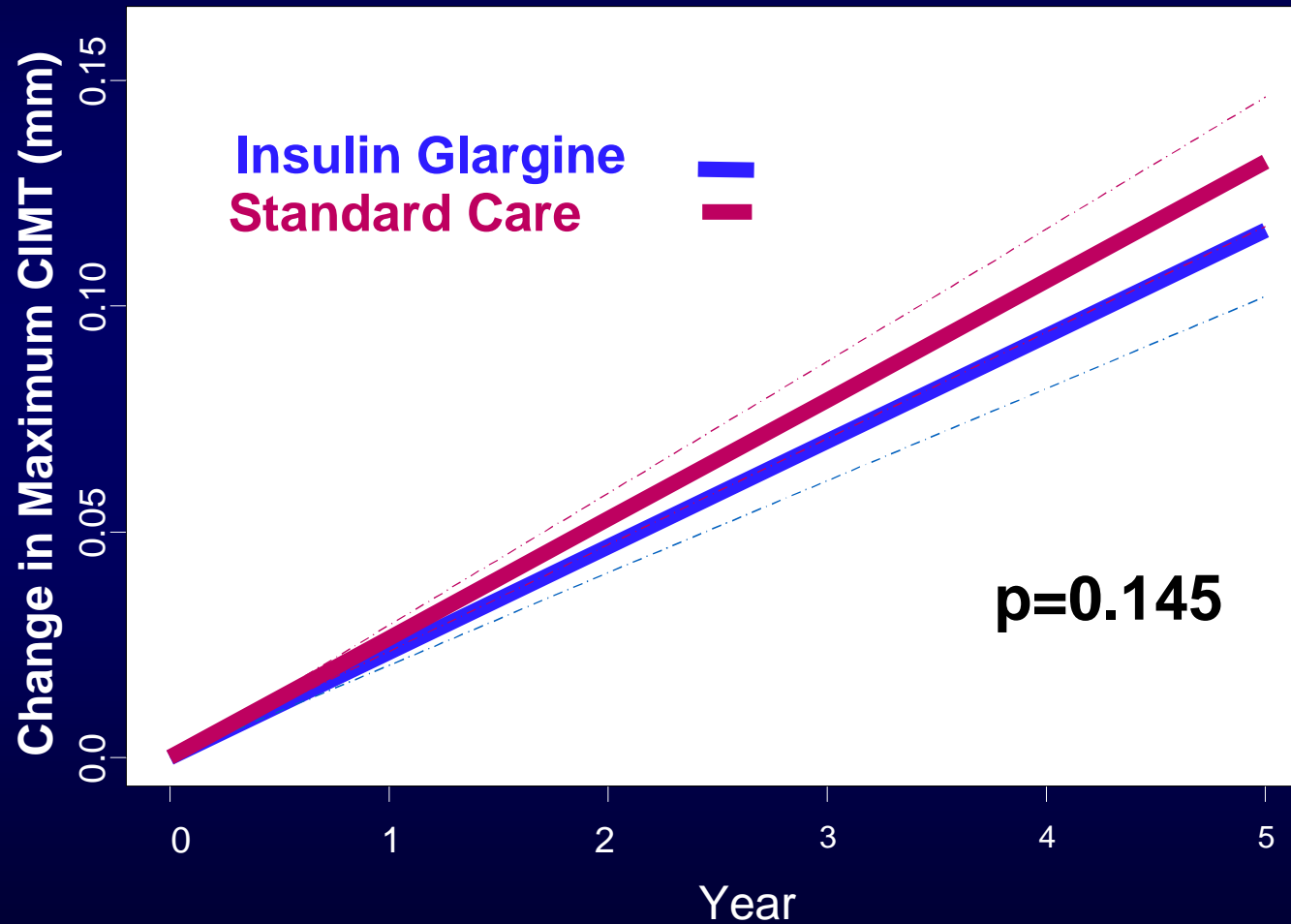
	HR (95% CI)	P	Insulin /100 py	Standard /100 py
1 <sup>st</sup> Coprimary	1.02 (0.94, 1.11)	0.63	2.94	2.85
2 <sup>nd</sup> Coprimary	1.04 (0.97, 1.11)	0.27	5.52	5.28
Microvascular Death	0.97 (0.90, 1.05) 0.98 (0.90, 1.08)	0.43 0.70	3.87 2.57	3.99 2.60
MI	1.02 (0.88, 1.19)	0.75	0.93	0.90
Stroke	1.03 (0.89, 1.21)	0.69	0.91	0.88
CV Death	1.00 (0.89, 1.13)	0.98	1.57	1.55
CHF Hospital	0.90 (0.77, 1.05)	0.16	0.85	0.95
Revascularized	1.06 (0.96, 1.16)	0.24	2.69	2.52



# Additional Outcomes



# Carotid IMT\* in ORIGIN: N=1091



# Glucose Lowering Drugs & Outcomes

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# CV Effects of GLP-1

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- GLP-1 receptors are widely expressed in the heart
- In LV dysfunction post MI, GLP-1 infusion may increase EF & reduce mortality (1-2 studies)
- GLP-1 & its analogs
  - *increases insulin secretion & reduces FFA*
  - *reduces glucagon*
  - *modestly lowers BP*
  - *reduces weight*
  - *improves endothelial function*

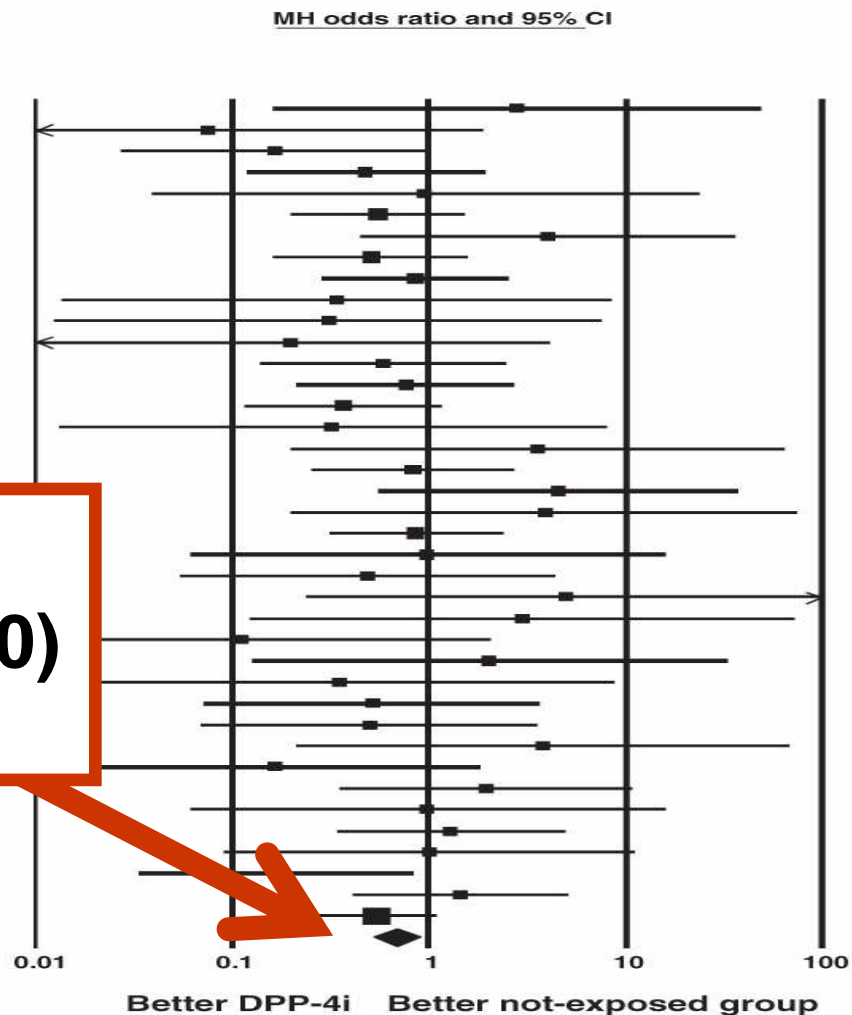


# Meta-analysis Small DPP4i Trials

Monami et al. Curr Med Res Op 2011

## Major Cardiovascular Events

Study name	Statistics for each study				
	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Pratley 2009 (a) (1)	2,822	0,161	49,496	0,710	0,478
Nauck 2009 (4)	0,076	0,003	1,879	-1,575	0,115
CV181-038 (8)	0,164	0,027	0,999	-1,961	0,050
Hollander 2010 (10)	0,477	0,118	1,931	-1,037	0,300
DeFronzo 2009 (11)	0,956	0,039	23,562	-0,028	0,978
Jadzinsky 2009 (12)	0,549	0,198	1,523	-1,151	0,250
NCT00698932 (13)	4,043	0,449	36,406	1,246	0,213
Chacra 2009 (14)	0,508	0,162	1,590	-1,164	0,245
Goke 2010 (15)	0,859	0,286	2,578	-0,271	0,787
NCT00305604 (13)	0,337	0,014	8,359	-0,664	0,506
NCT01028391 (13)	0,309	0,012	7,643	-0,717	0,473
Yoon 2011 (18)	0,197	0,009	4,122	-1,047	0,295
Visboll 2010 (19)	0,591	0,140	2,492	-0,717	0,473
Charbonnel 2006 (20)	0,763	0,213	2,731	-0,416	0,678
Aschner 2006 (21)	0,364	0,114	1,158	-1,712	0,087
Raz 2008 (22)	0,323	0,013	8,029	-0,689	0,491
Raz 2006 (23)	3,543	0,198	63,368	0,860	0,390
NCT00482729 (13)	0,827	0,251	2,723	-0,313	0,754

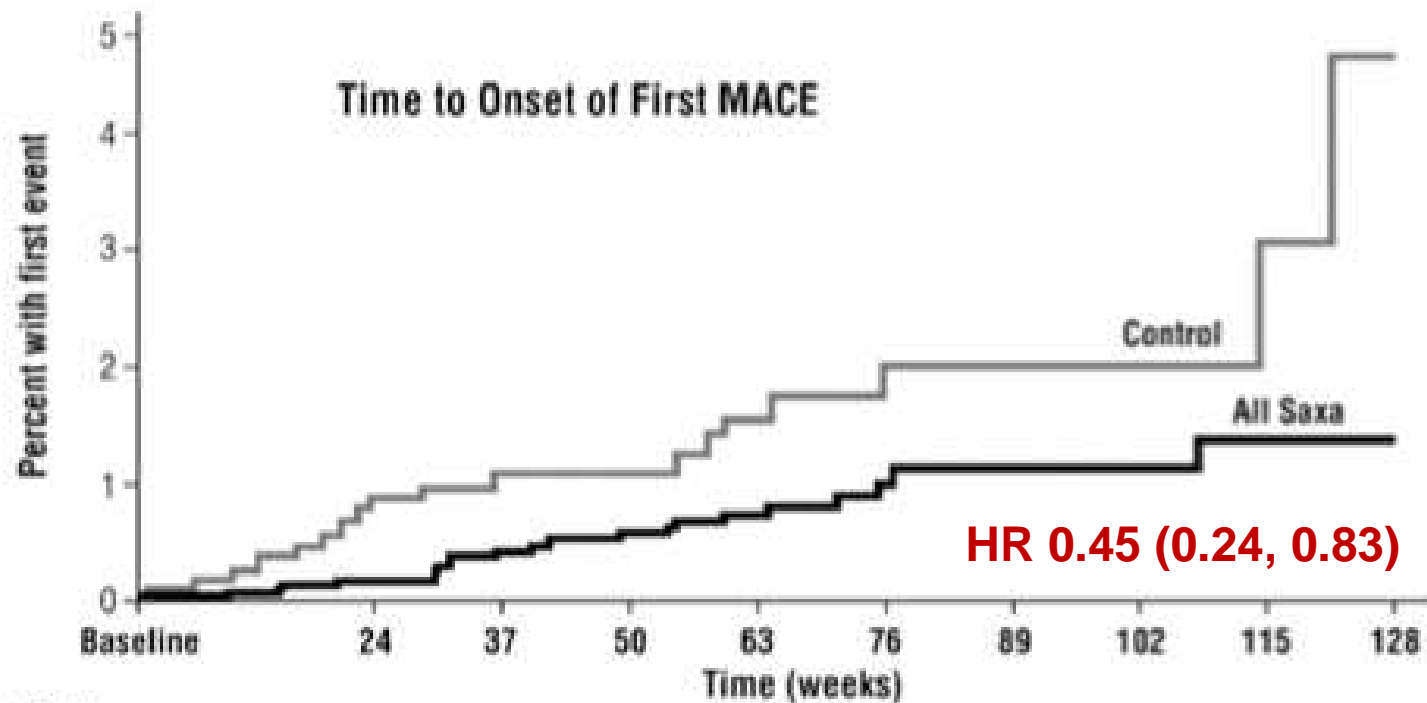


**Overall  
OR = 0.69 (95%CI 0.53, 0.90)  
P=0.006**

Scherbaum 2008 (39)	1,947	0,351	10,793	0,763	0,446
Schweizer 2009 (40)	0,982	0,061	15,833	-0,013	0,990
Schweizer 2007 (41)	1,292	0,340	4,912	0,376	0,707
Pan 2008 (42)	1,000	0,090	11,089	0,000	1,000
Rosenstock 2007 (a) (44)	0,168	0,034	0,840	-2,173	0,030
Filozof 2010 (45)	1,450	0,407	5,169	0,573	0,567
Ferrannini 2009 (46)	0,540	0,266	1,096	-1,706	0,088
<b>Overall</b>	<b>0,689</b>	<b>0,528</b>	<b>0,899</b>	<b>-2,747</b>	<b>0,006</b>

# Meta-analysis Small Saxa Trials

Sciricca et al. AM Heart J 2011; 818 (n=41 MACE)



Patients at Risk

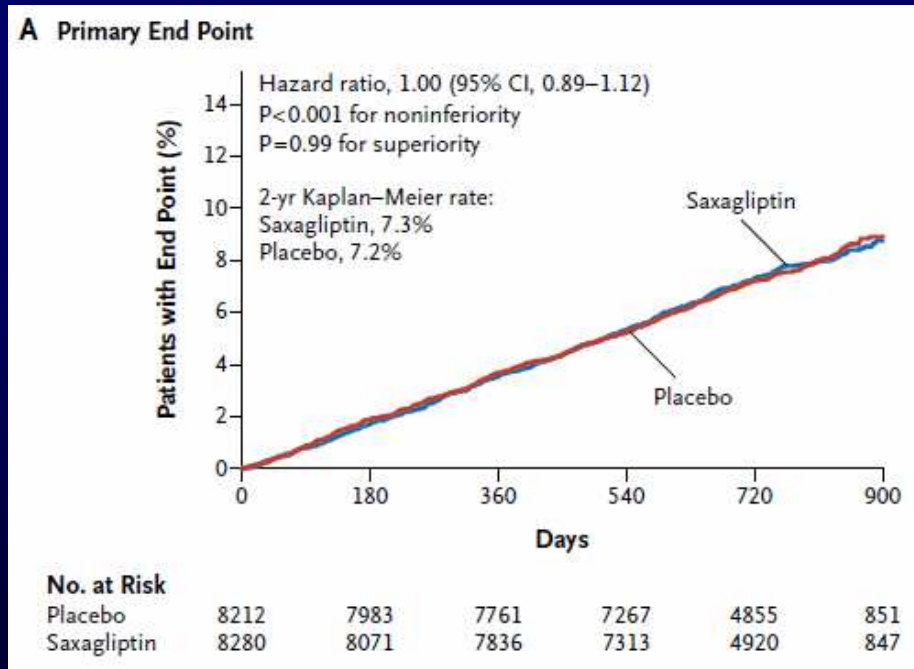
Control	1251	935	860	774	545	288	144	123	102	57
All Saxa	3356	2615	2419	2209	1638	994	498	436	373	197

# Saxagliptin: T2DM & CV Risk

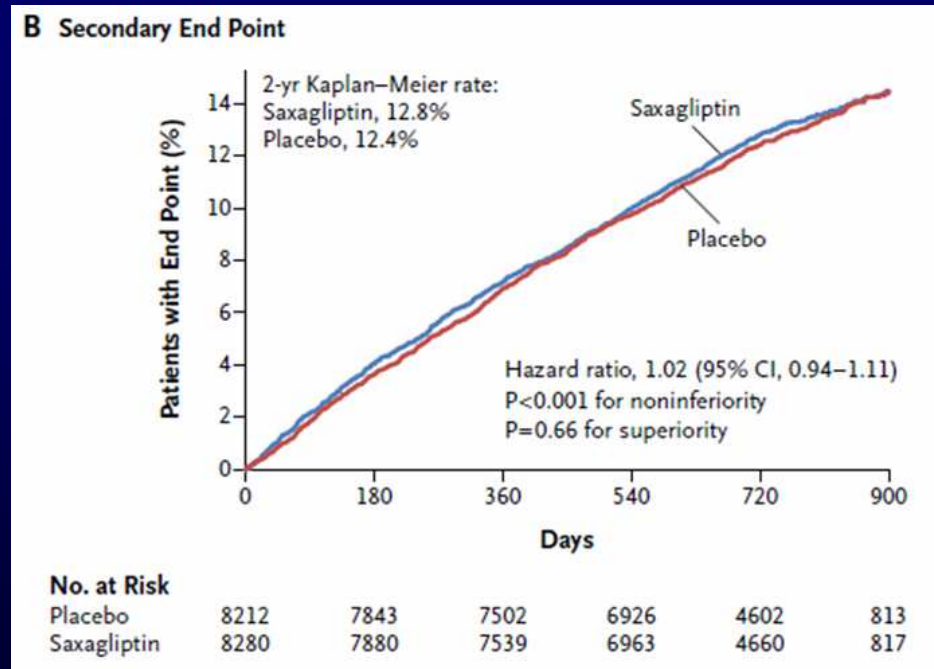
SAVOR-TIMI 53 study NEJM 2013

- N = 16,492 men & women with CVD or risk factors
- Saxagliptin 5 mg/d or placebo (2.5 mg/d if eGFR < 50)
- Median F/U = 2.1 yrs

1<sup>o</sup> Outcome: CV Death, MI, Isch.Stroke

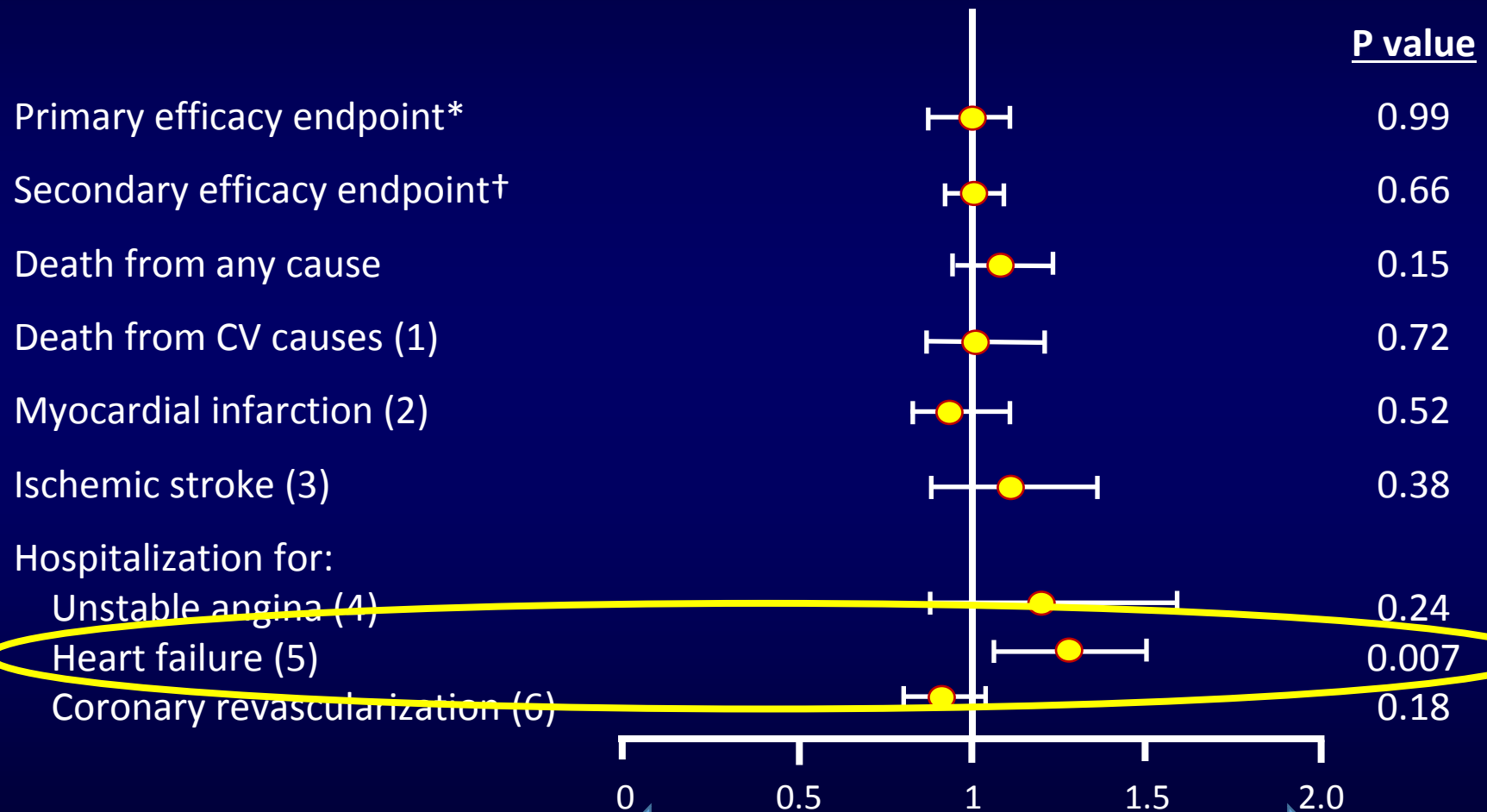


2<sup>o</sup> Outcome: 1<sup>o</sup> or hosp UA, CHF, revasc



# SAVOR: Other Outcomes

NEJM 2013



\*Composite of 1, 2 and 3

†Composite of 1–6

Saxagliptin better

Hazard ratio  
(95% CI)

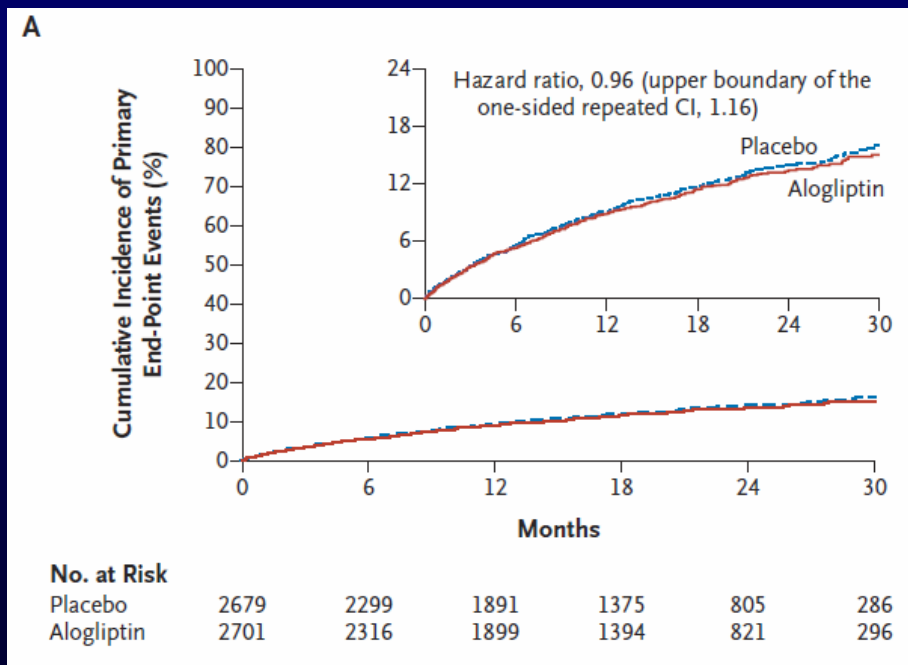
Placebo better

# Alogliptin: T2DM + MI or UA

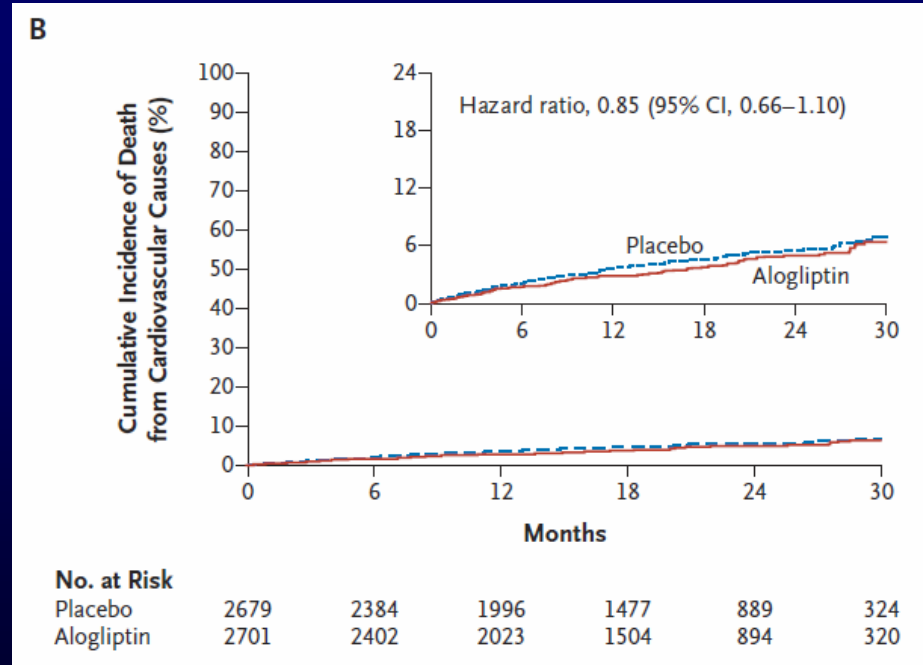
EXAMINE study NEJM 2013

- N = 5380 men & women with ACS 15-90 d before rand
- Alogliptin 25 mg/d or placebo (12.5 mg/d if eGFR 30-60; 6.25 if < 30)
- Median F/U = 1.5 yrs

## 1<sup>o</sup> Outcome: CV Death, MI, Stroke



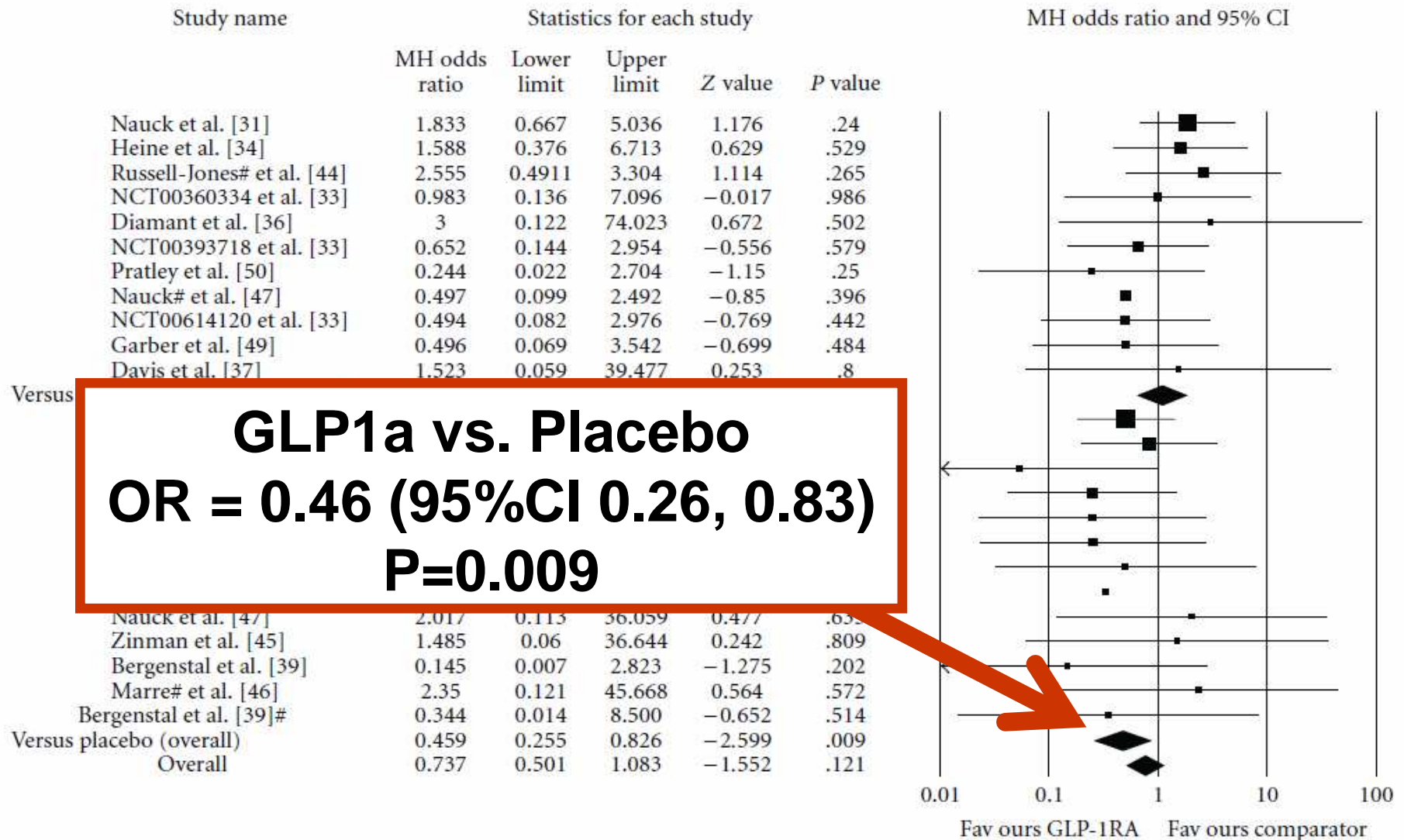
## Death from CV causes



MI = myocardial infarction; UA = unstable angina

# Meta-analysis Small GLP1a Trials

Monami et al. Exp Diab Res 2011



# Glucose Lowering Drugs & Outcomes

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# What about Lifestyle Therapies?

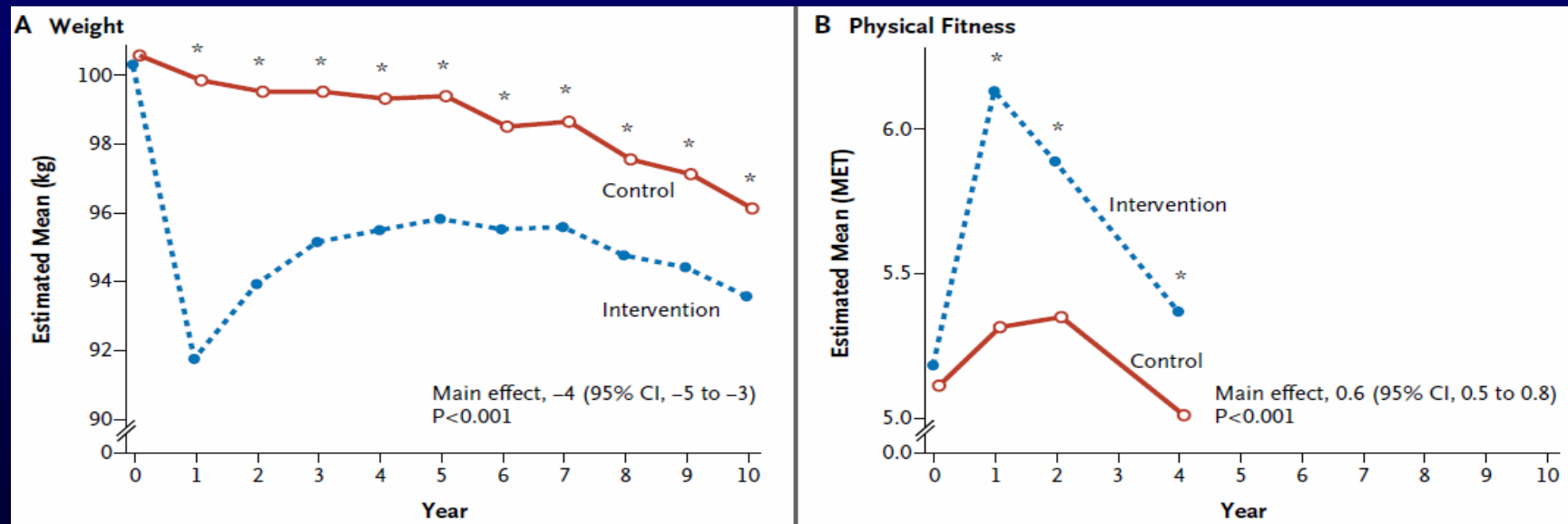
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- In people with diabetes?
- To prevent diabetes?

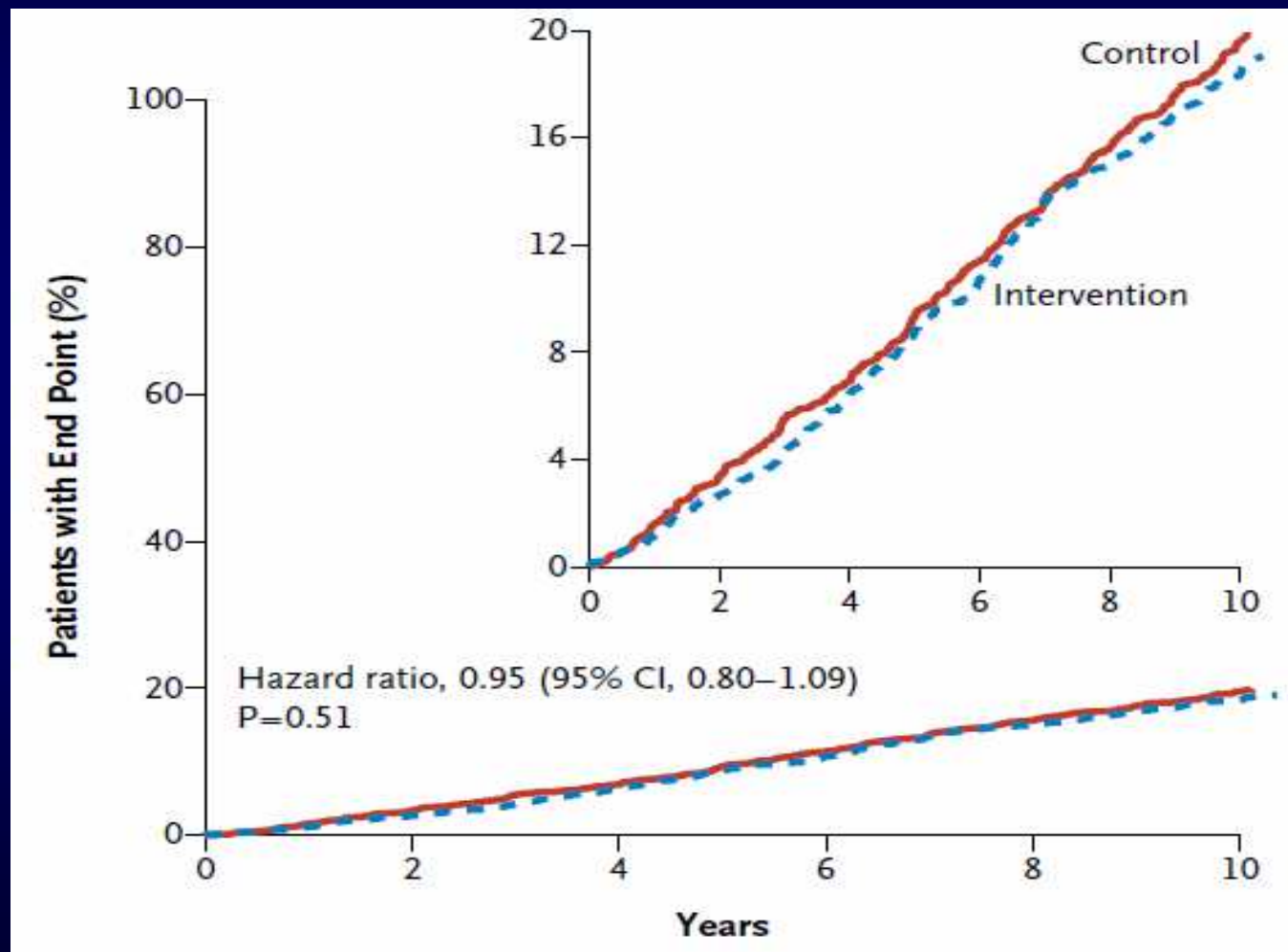


# Look AHEAD Multicenter RCT (Look for Action for Health in Diabetes)

- 5145 overweight/obese individuals with type 2 DM
- 59.5% female; mean age 58.7 years
- Interventions: usual care + either.....
  - *Intensive lifestyle intervention (ILI)* OR



# Look AHEAD Multicenter RCT (Look for Action for Health in Diabetes)



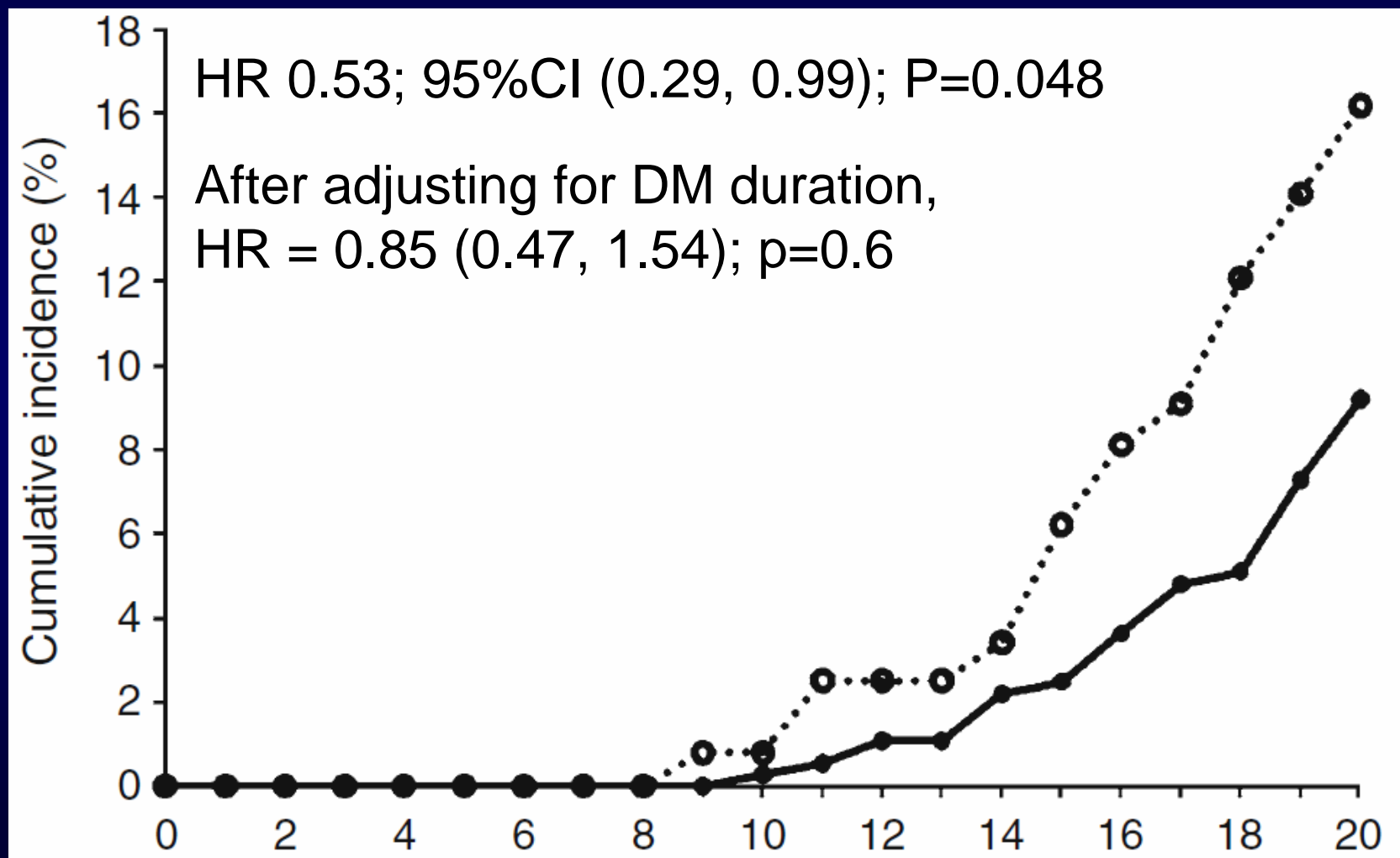
# What about Lifestyle Therapies?

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- In people with diabetes?
- To prevent diabetes?

# 20 Yr Risk of Severe Retinopathy

Laser, Blindness or Proliferative Retinopathy



# Ongoing Large CV Outcomes Trials of Anti-diabetic Agents

Class	Participants	Drugs	Est. N
DPP4i	Diabetes	sitagliptin, linagliptin, omarigliptin	30,000
GLP1a	Diabetes	lixisenatide, liraglutide, exenatide (extended) dulaglutide, semaglutide	40,000
SGLT2i	Diabetes	canagliflozin, empagliflozin, dapagliflozin	25,000
AGI	IGT	acarbose	7,500
TZD	Insulin Resistant	pioglitazone	4,000

# Summary of the Best RCT Evidence

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- *Intensive glucose lowering **in new type 2 DM** reduces long-term risk of CVD & mortality*
- *Intensive glucose lowering in **advanced type 2 DM** has modest CVD benefits but ACCORD noted a mortality risk after 3.5 yrs*
- *2 commonly used strategies to lower glucose (insulin sensitization vs. provision) have similar effects on CVD*

# Summary of the Best RCT Evidence

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- *Metformin may have a mortality benefit*
- *Lifestyle approaches may not be better than drugs*
- *Several ongoing studies are testing novel strategies*
- *This research is crucial because....*

*We are always certain how to treat our patients...  
when we have no data.....*

# Final Word – Applying the Evidence

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The Evidence shows what does & does not work to reduce serious outcomes in the “average patient”

*little judgment is required to interpret*

The specific patient in front of you is not the “average patient”

*much judgment is required to assess*

***Clinical decisions for that patient are best based on judgment that is informed by the best evidence***

*Evidence without the judgment →*

*A technician*

*Judgment without the evidence →*

*A friend.....*

*Both evidence and judgment →*

*A Physician..*