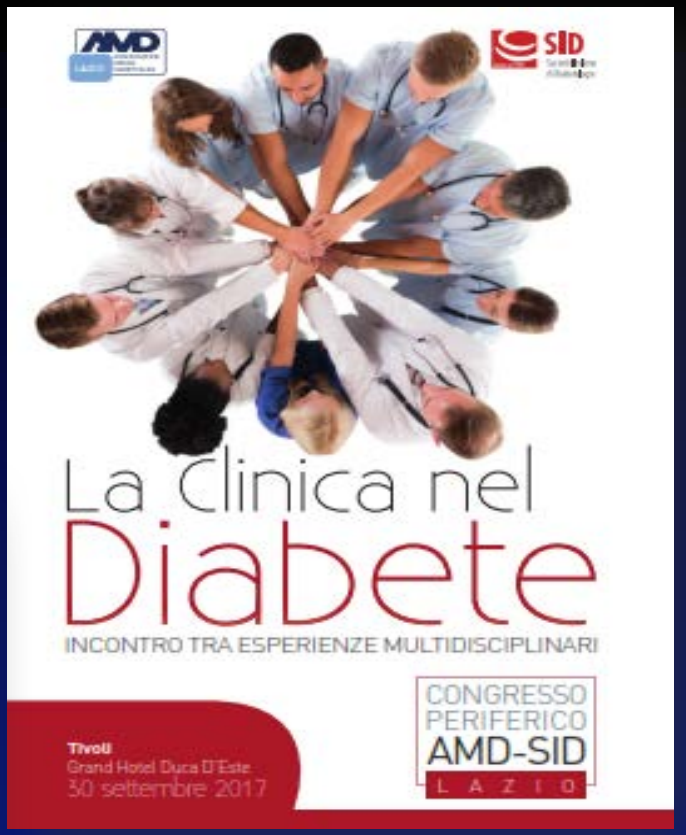
Farmaci Antidiabetici e Rischio Cardio-Nefro-Vascolare



Il Fatto

A. Giaccari

CONGRESSO PERIFERICO AMD - SID

LA CLINICA DEL DIABETE INCONTRO TRA ESPERIENZE MULTIDISCIPLINARI

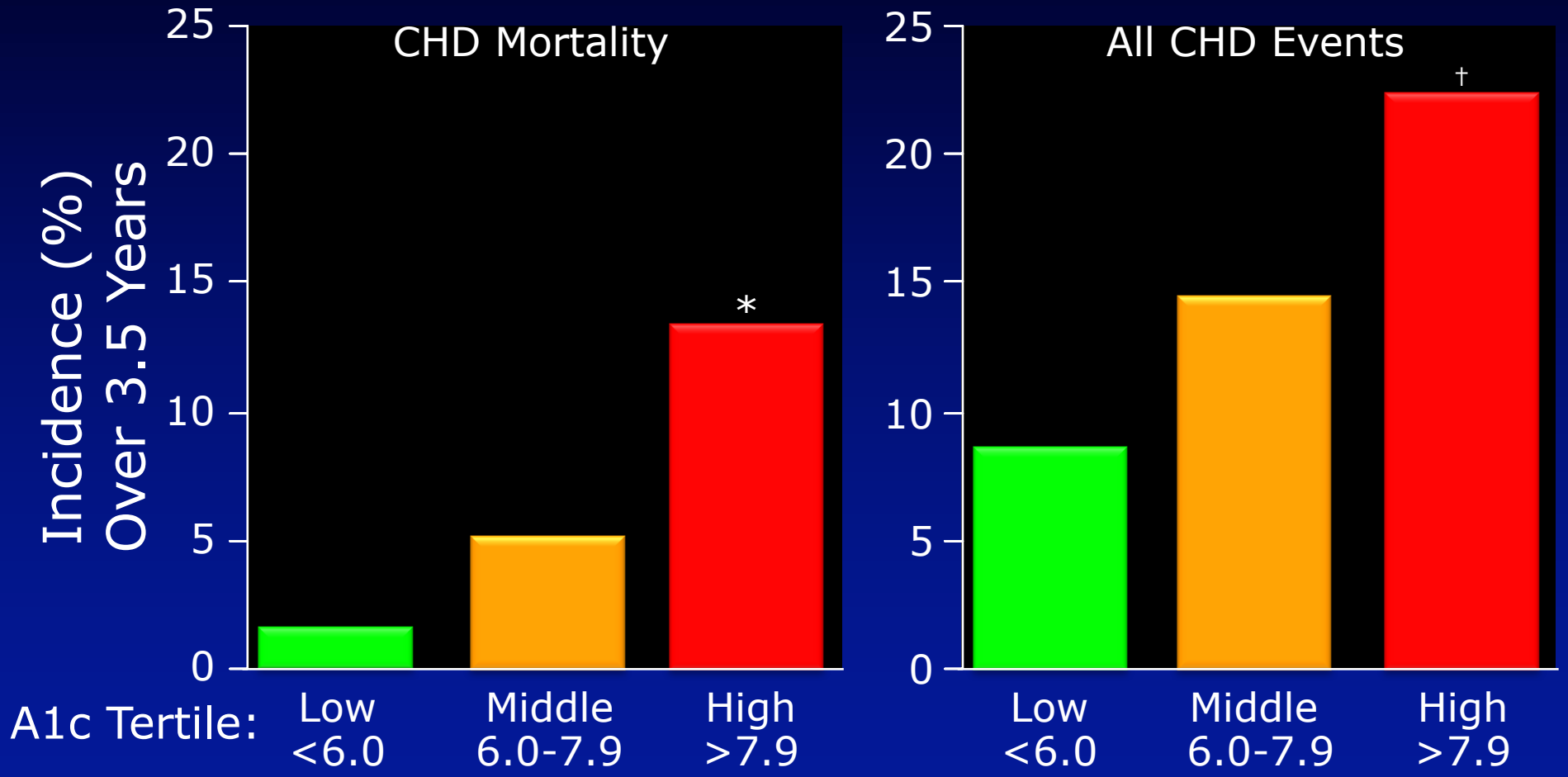
Tivoli, 30 settembre 2017

Il dr. GIACCARI dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- ASTRAZENECA, LILLY, TAKEDA
  SANOFI, MSD

A1c Predicts CV Risk

prospective study of 229 Finnish type 2 diabetic patients without previous vascular disease



A1c = glycosylated hemoglobin; CHD = coronary heart disease.
*$P<0.01$ vs lowest tertile; †$P<0.05$ vs lowest tertile.

Kuusisto J et al. Diabetes 43:960, 1994

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*

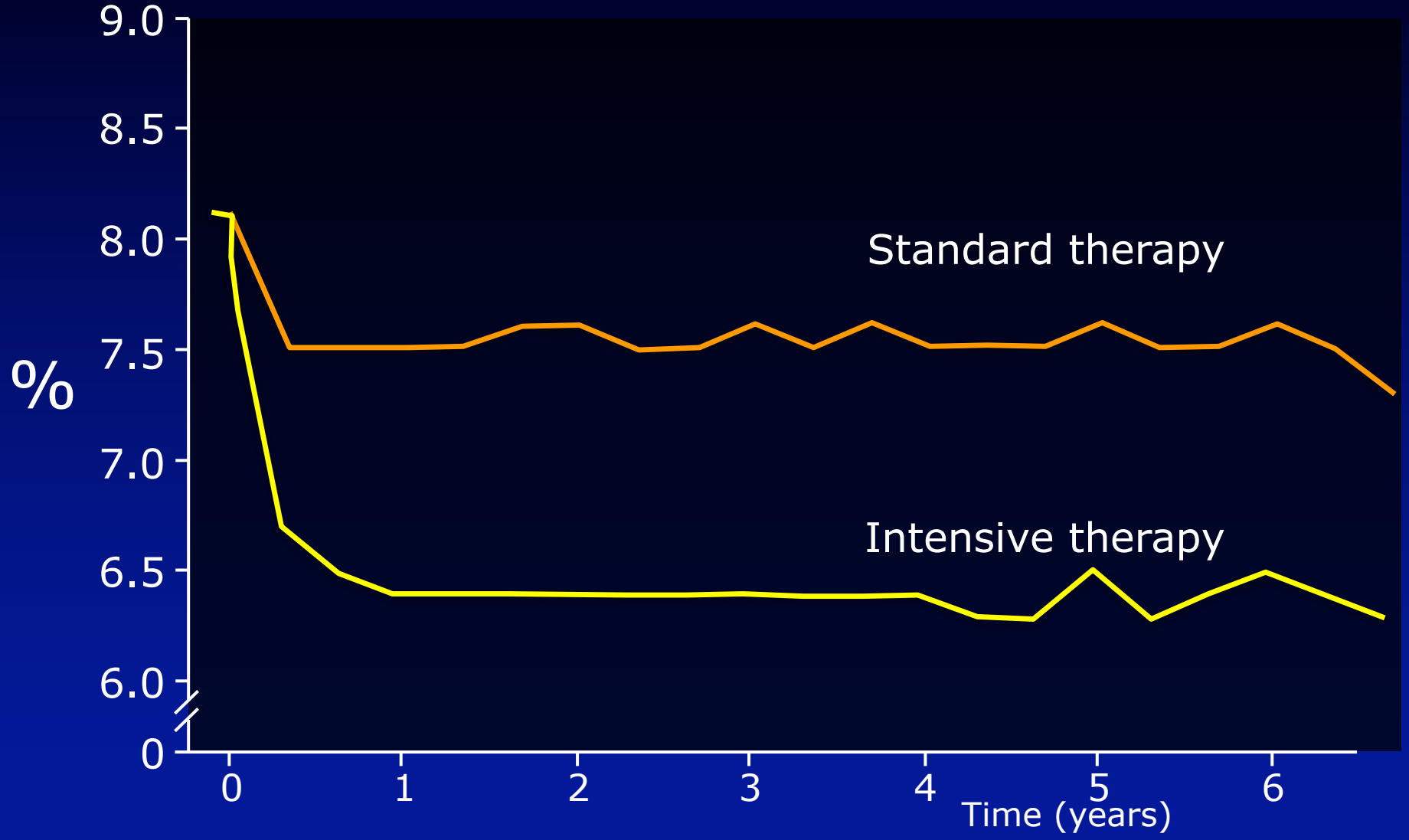
Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

N ENGL J MED 360;2 NEJM.ORG JANUARY 8, 2009

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

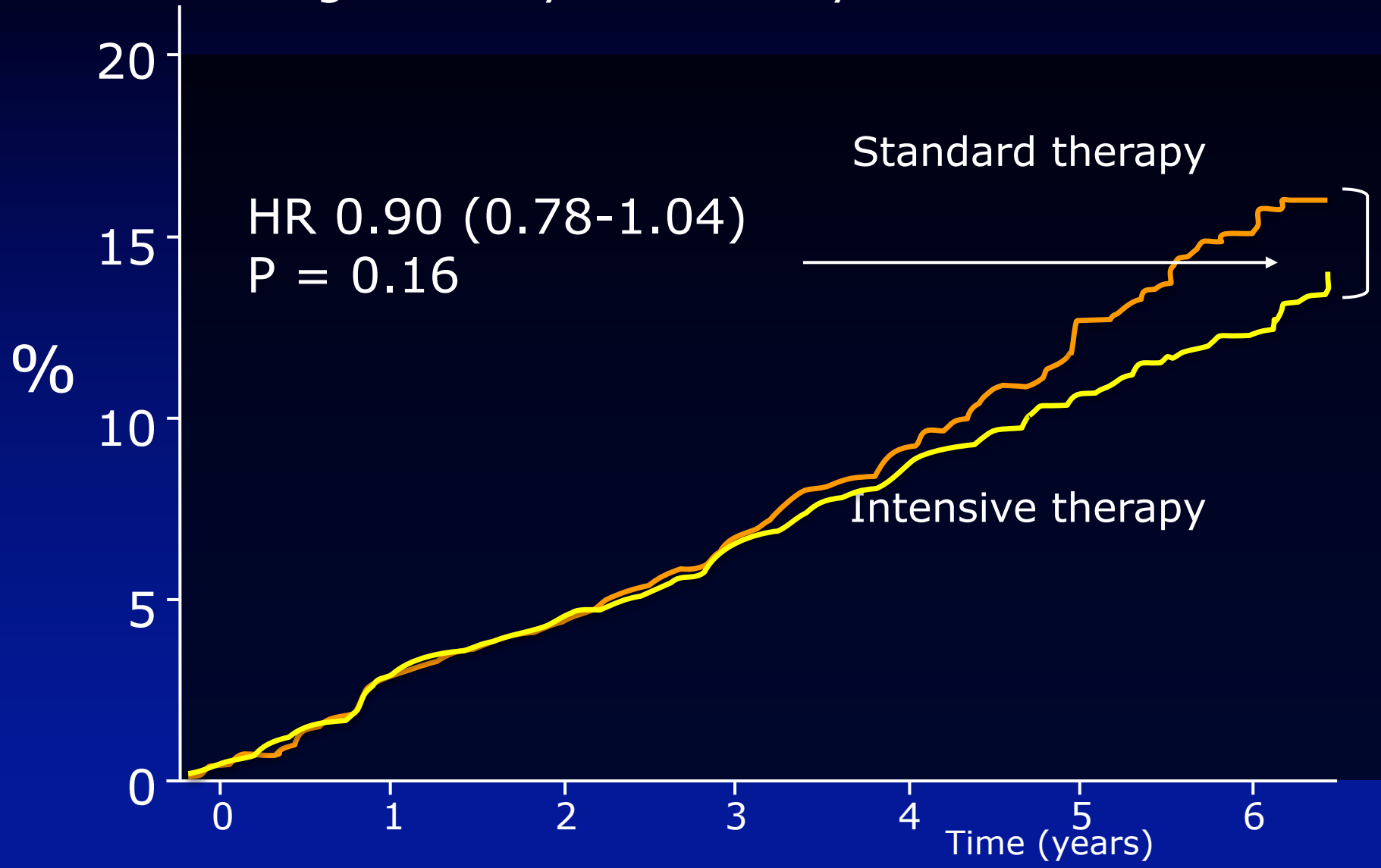
ACCORD: HbA1c



ACCORD Study Group. *N Engl J Med.* 2008;358:2545-59.

ACCORD: CV Events

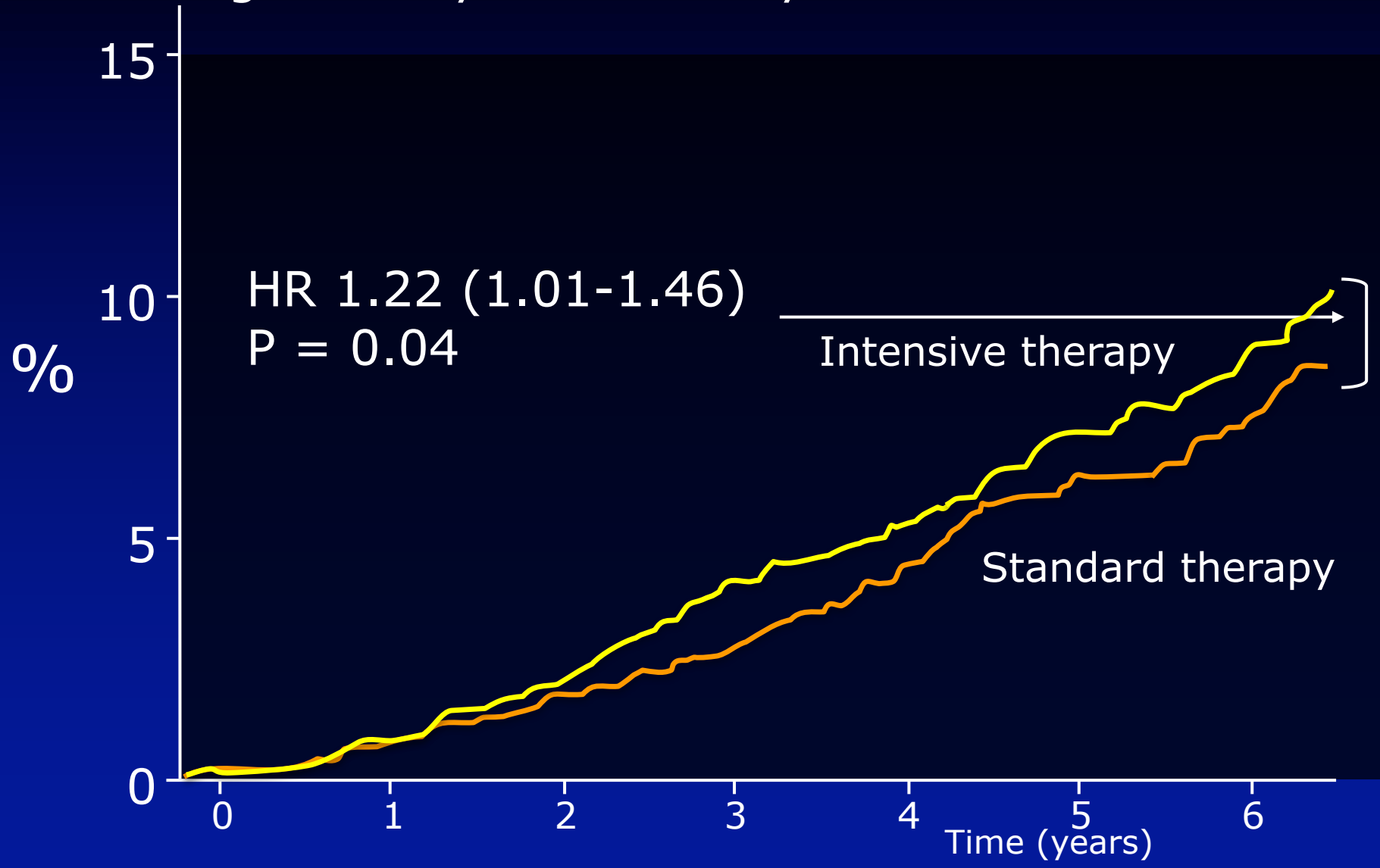
were non-significantly reduced by intensive treatment



ACCORD Study Group. *N Engl J Med.* 2008;358:2545-59.

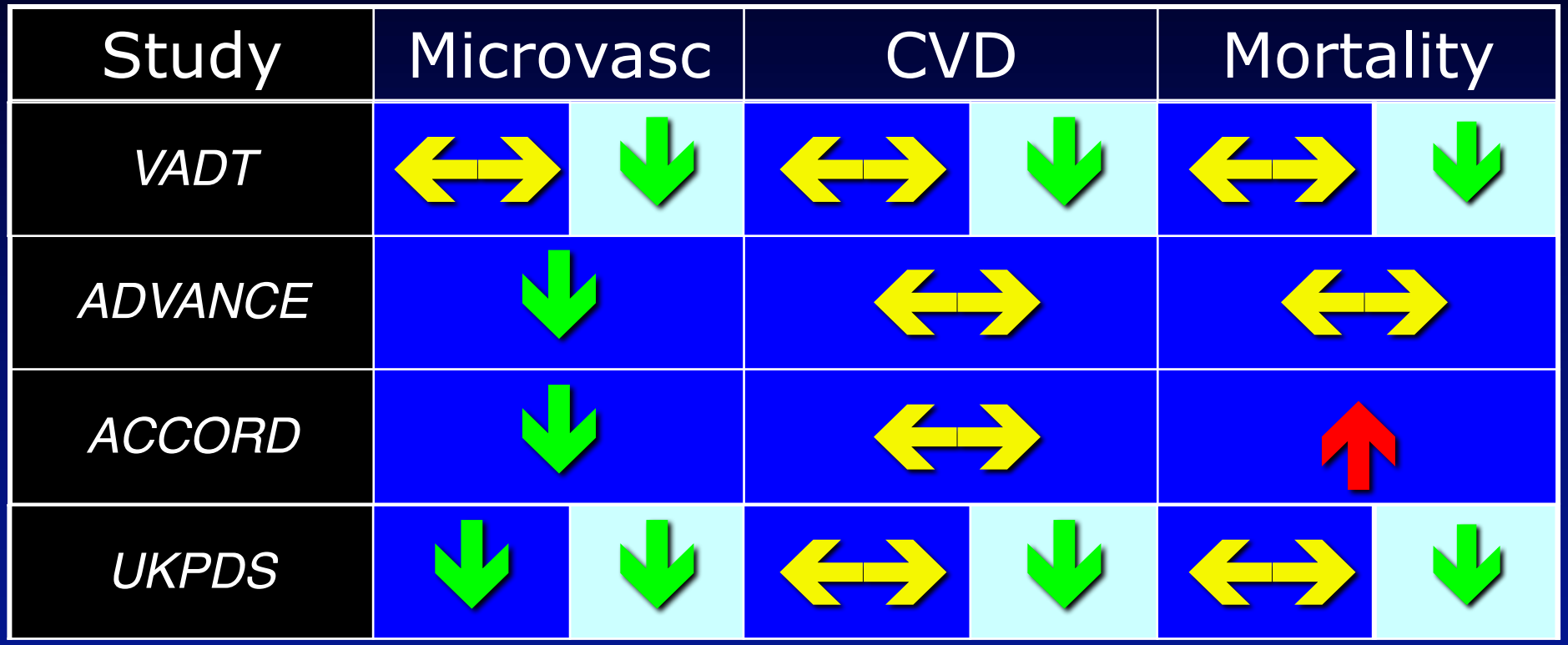
ACCORD: all cause mortality

was significantly increased by intensive treatment



ACCORD Study Group. *N Engl J Med.* 2008;358:2545-59.

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

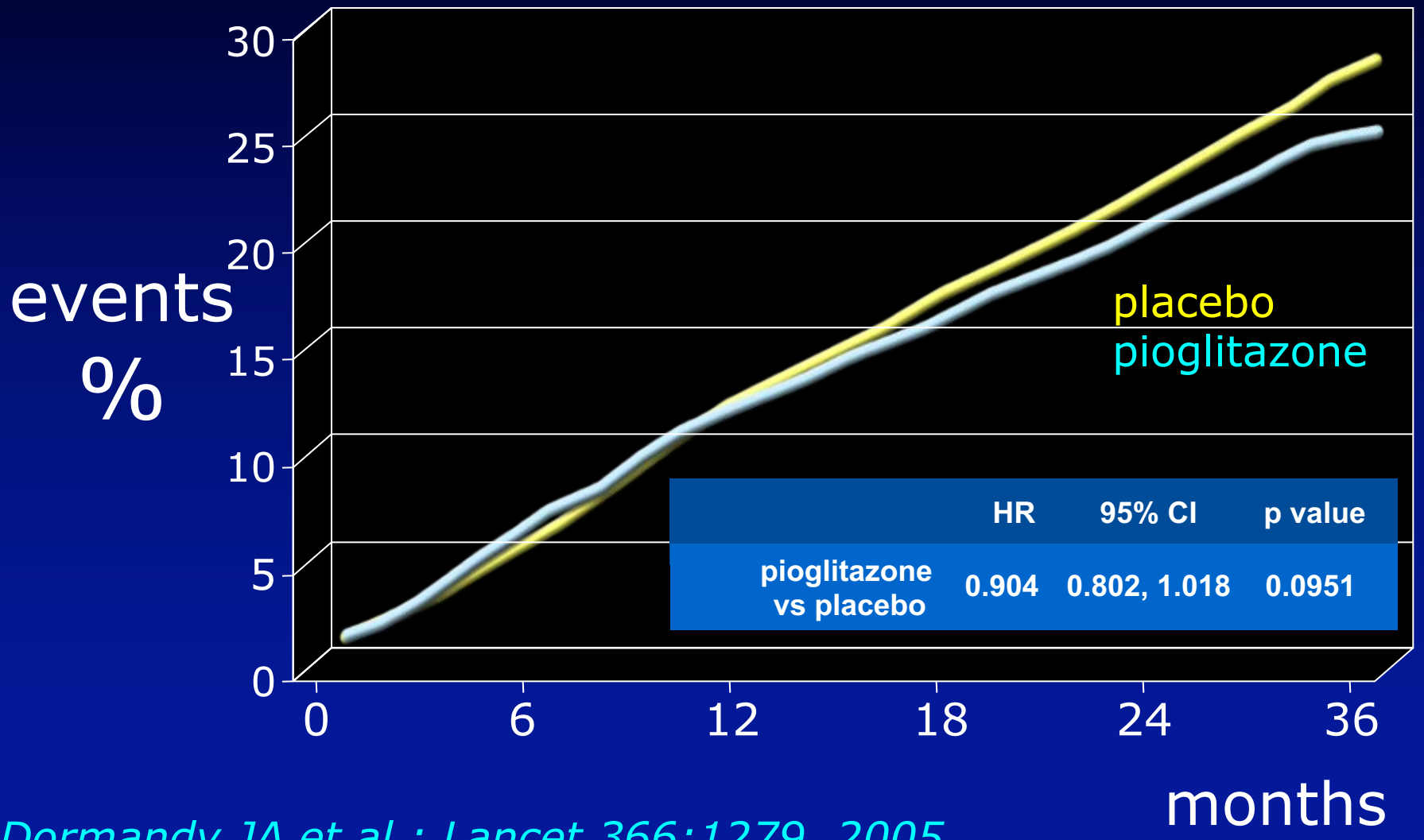


Kendall DM, Bergenstal RM. © International Diabetes Center 2008
UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854-865.
Nathan DM, et al. N Engl J Med. 2005;353:2643-2653. Gerstein HC, et al. N Engl J Med. 2008;358:2545-2559.
Patel A, et al. N Engl J Med. 2008;358:2560-2572. Duckworth W et al. N Engl J Med 2009;360

Initial Trial

Long Term Follow-up

PROACTIVE: primary outcome

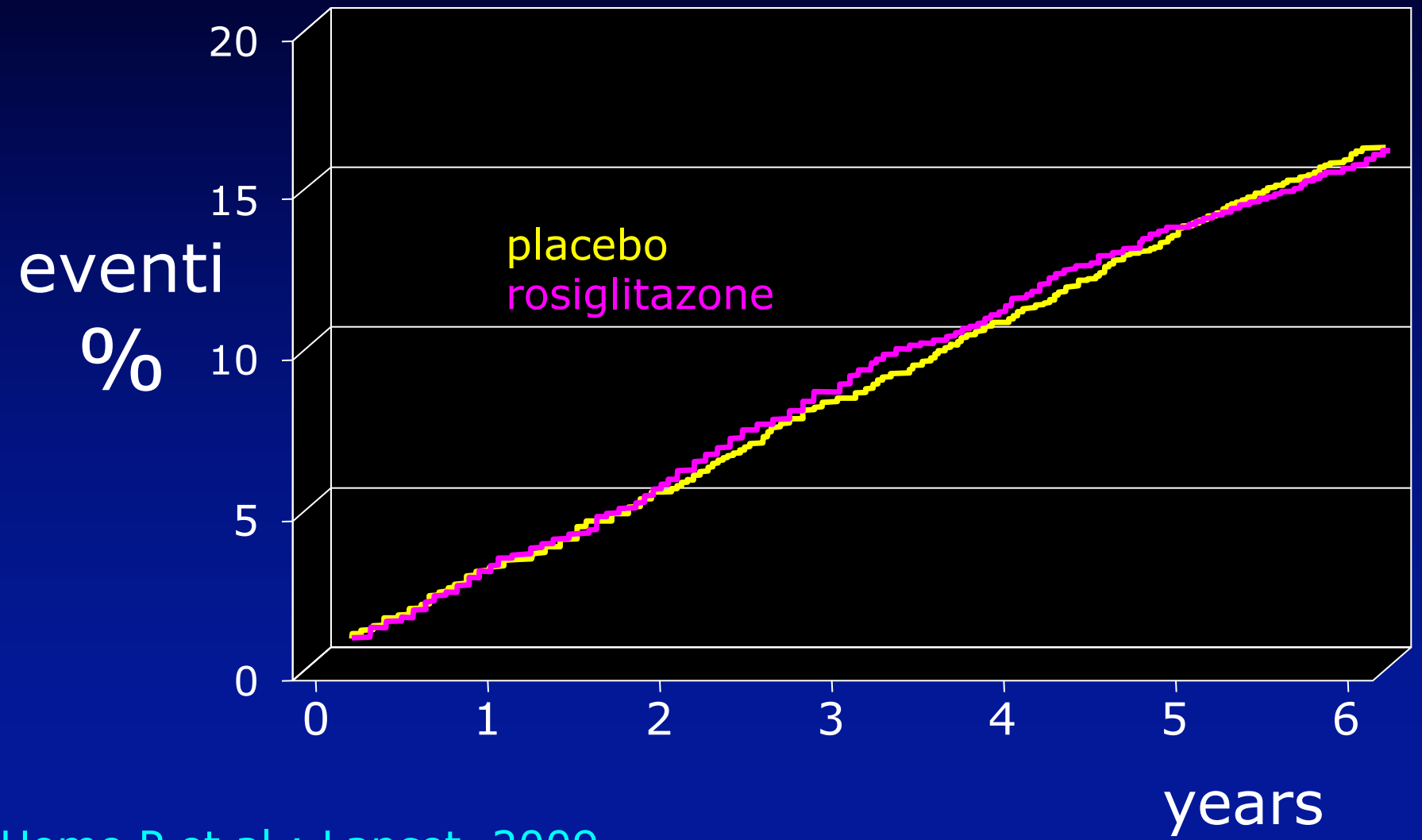


	HR	95% CI	p value
pioglitazone vs placebo	0.904	0.802, 1.018	0.0951

Dormandy JA et al.: Lancet 366:1279, 2005

RECORD primary endpoint

CV events and hospitalizations



Home P et al.: Lancet, 2009

rosiglitazone: the final meta-analysis for MI

RECORD

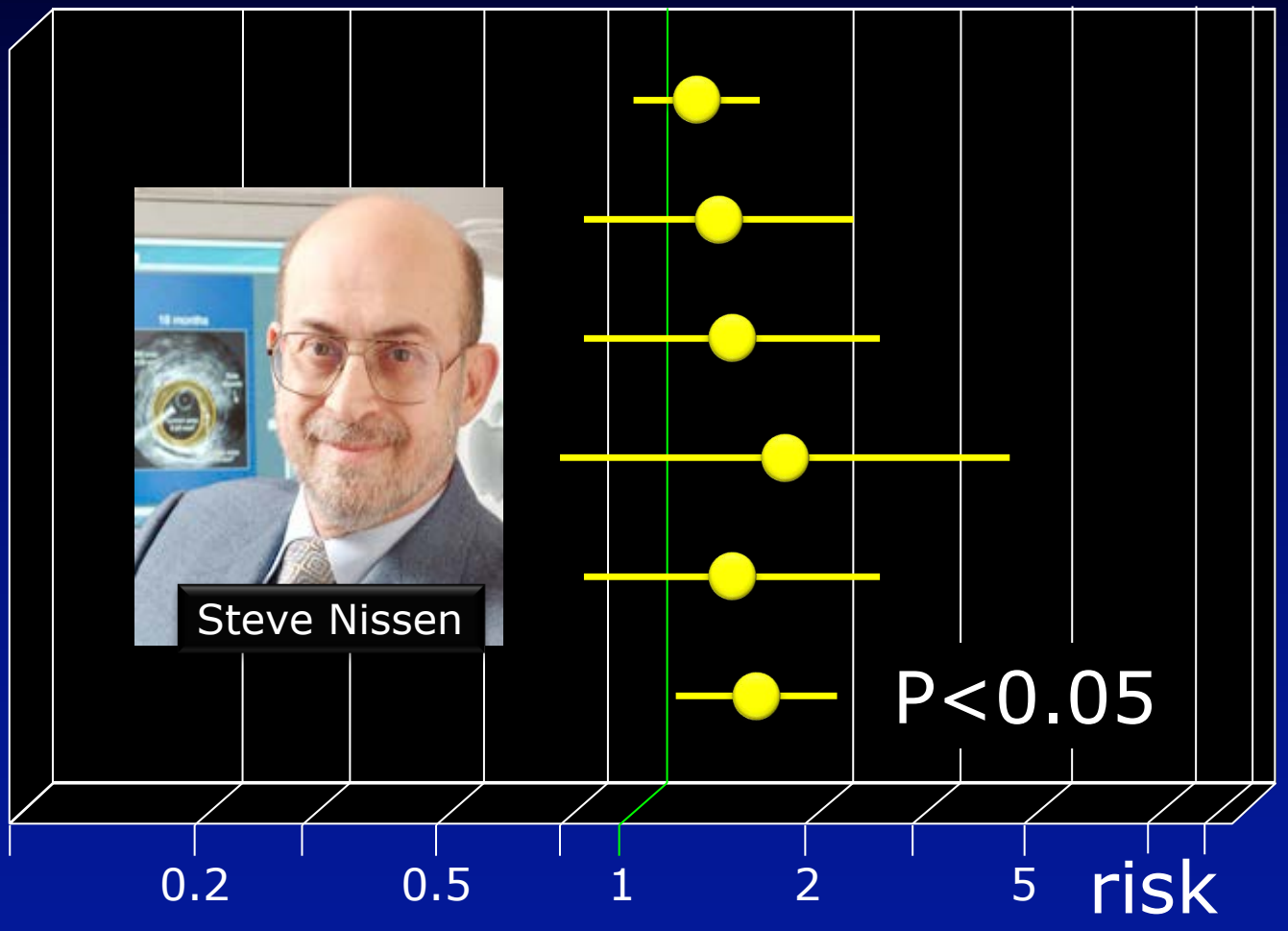
ADOPT

DREAM

3 arms

2 arms

all



Nissen SE & Walski K: Arch Intern Med 170:1191, 2010

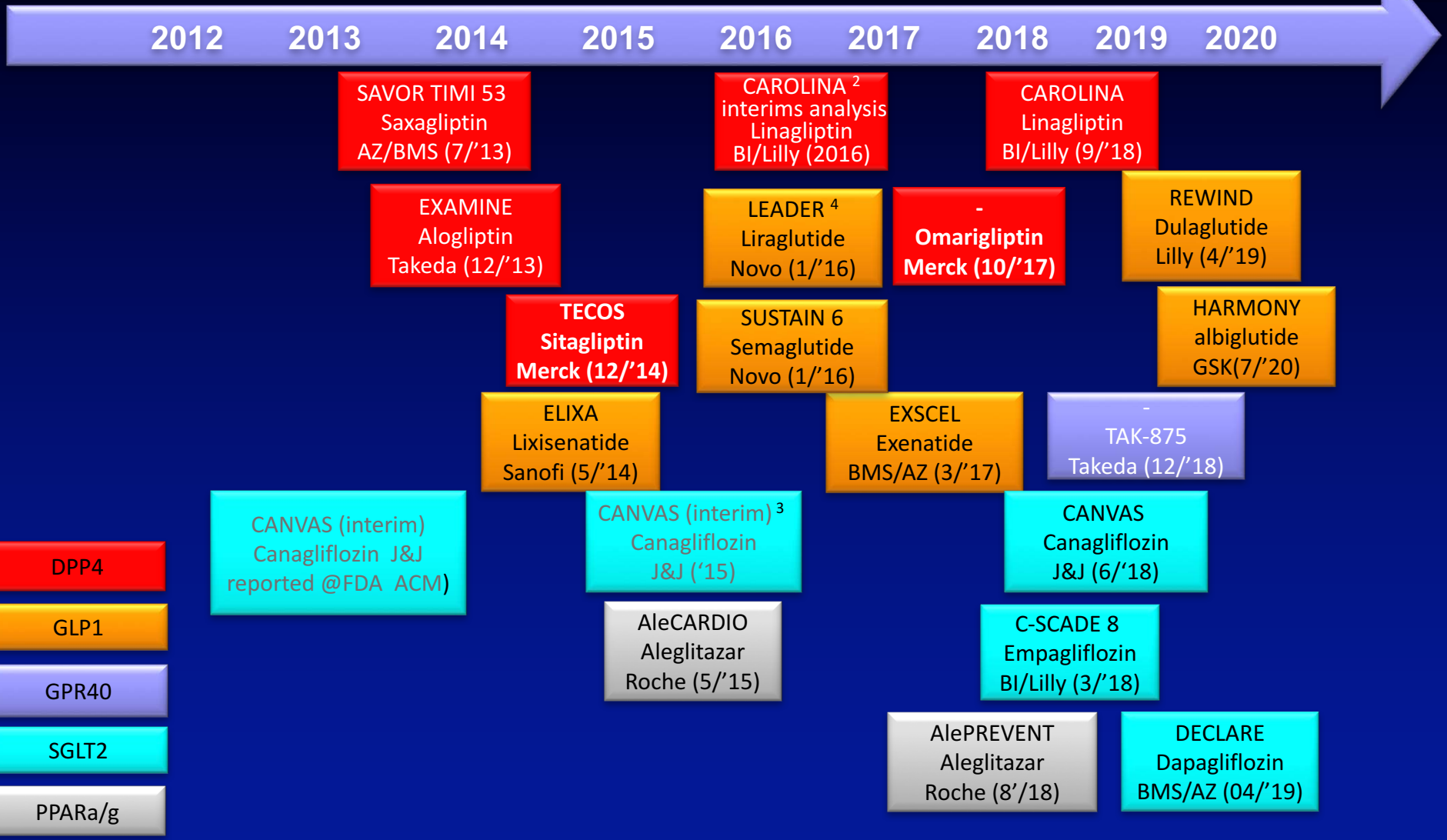

ROSIGLITAZONE
2000-2010
promised to save ß-cells
executed on charges of murder

the burdening clinical point

can the reduction of HbA1c
prevent CV events?

NO!
they might even be dangerous

CV outcome trials for new drugs [1]



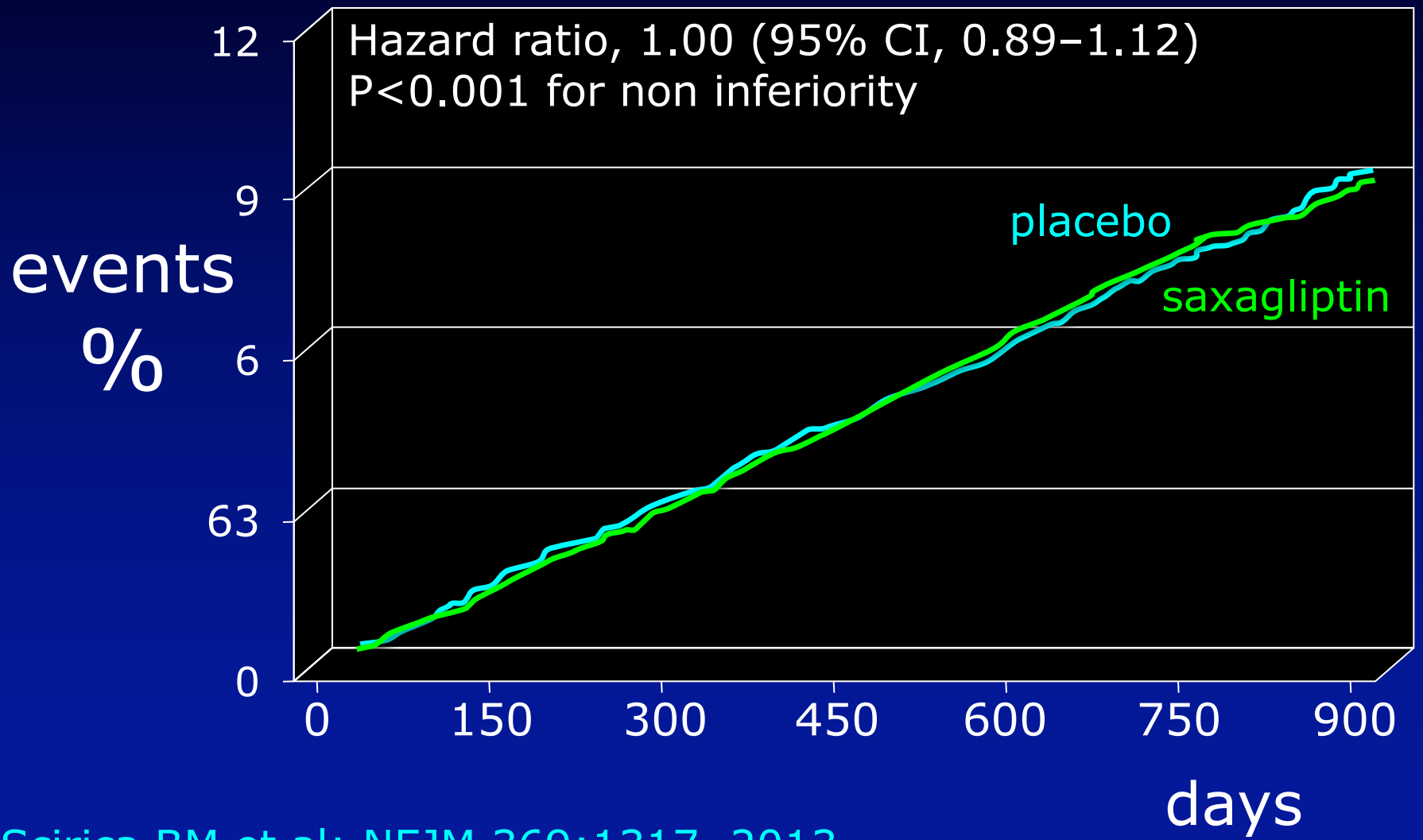
[1] Expected dates for completion of primary endpoint (source: clinicaltrials.gov, accessed 04/2016)

[2] Interims data ~2016; 2nd Linagliptin CV outcomes trial vs PBO (CARMELINA) expected to start in 2013, per primary CI (tbc) results in 2018

[3] Per Janssen commentary at FDA ACM, next CV meta-analysis planned after 500 events- expected in 2015

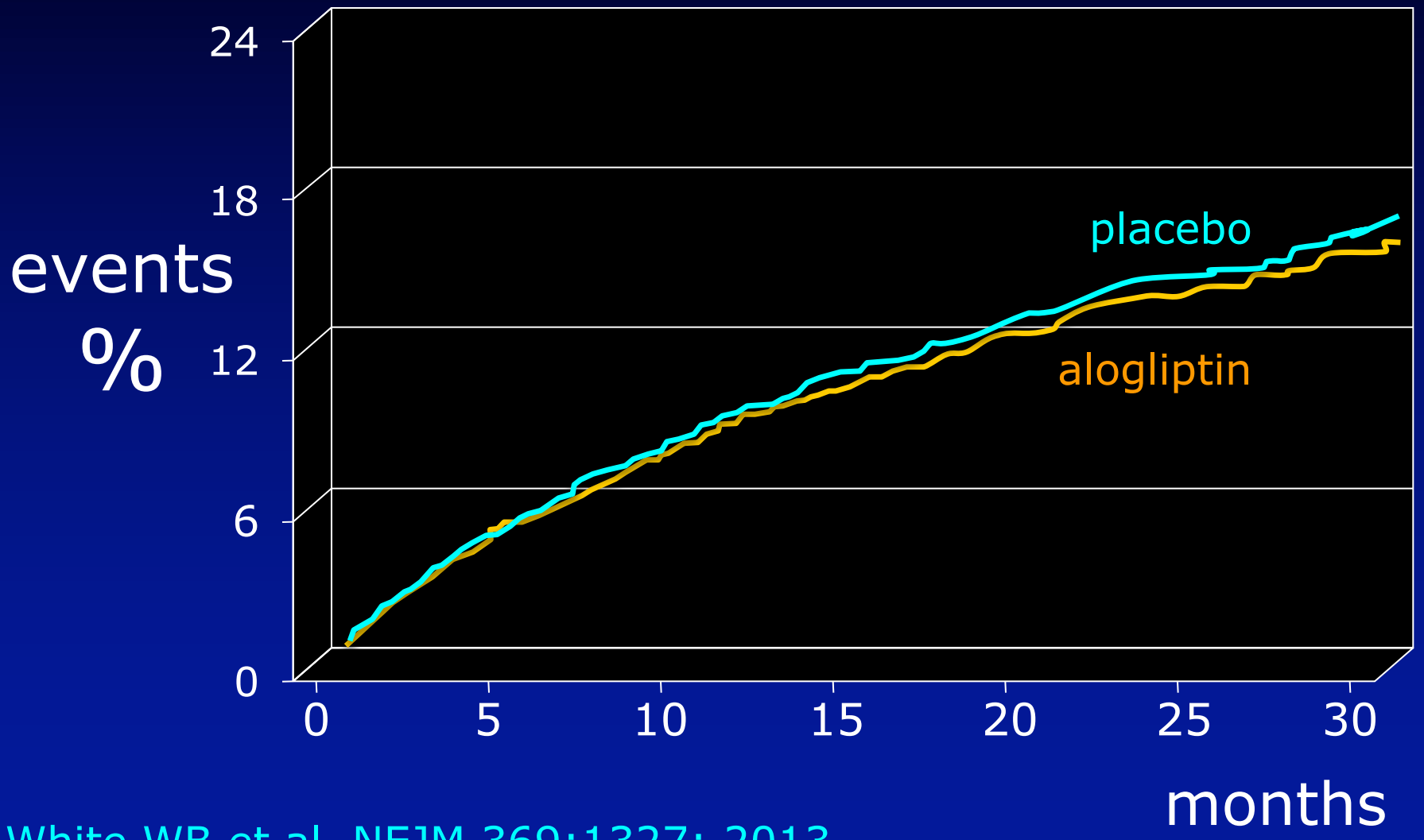
[4] per Novo interims analysis possible in 2014/15 if required for review of obesity sNDA

SAVOR-TIMI: MACE cumulative incidence



Scirica BM et al: NEJM 369:1317, 2013

EXAMINE: MACE cumulative incidence



White WB et al. NEJM 369:1327; 2013

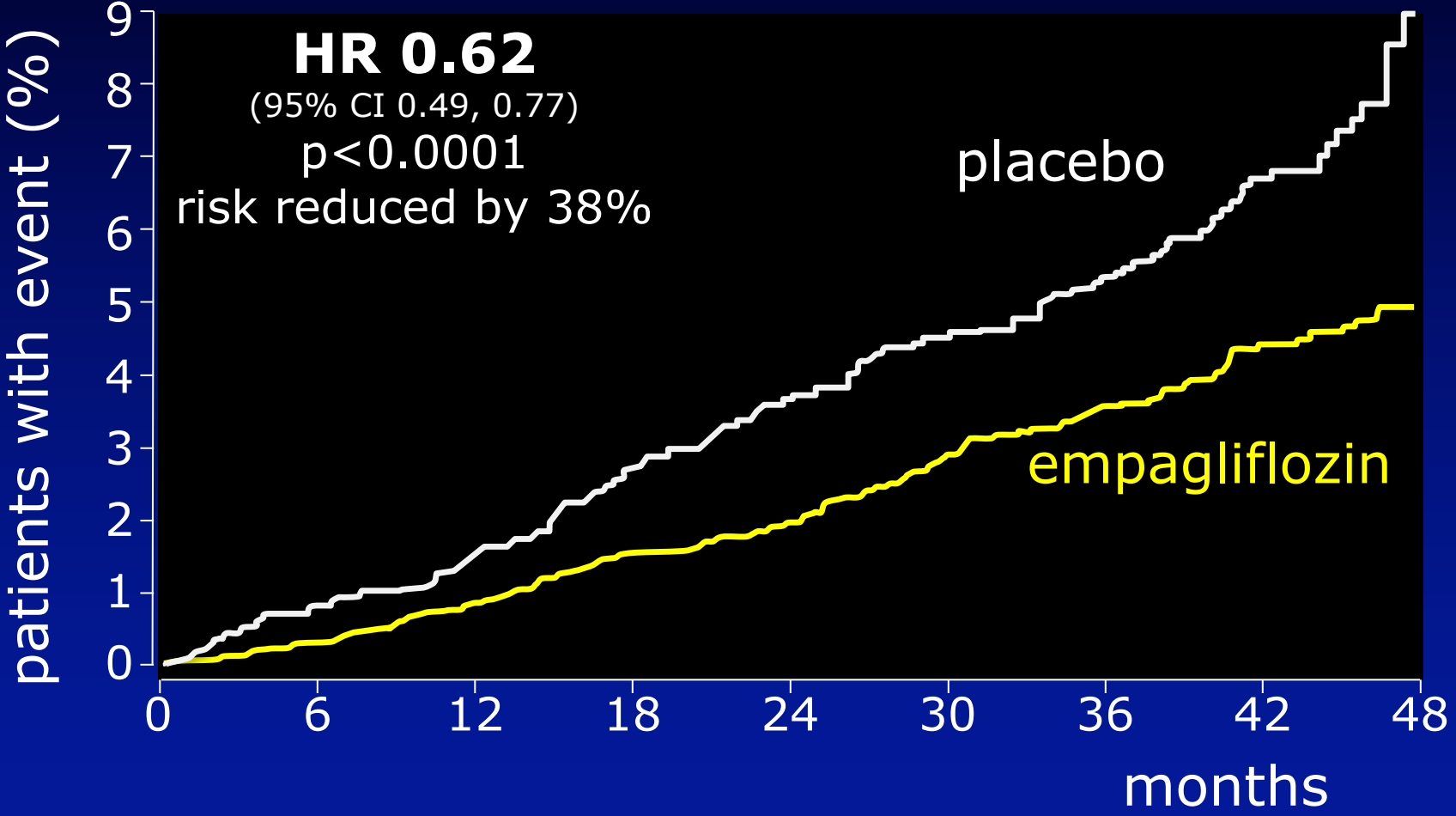
TECOS: Primary CV Outcome
PP Analysis for Non-inferiority

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

Green JB et al. NEJM 2015

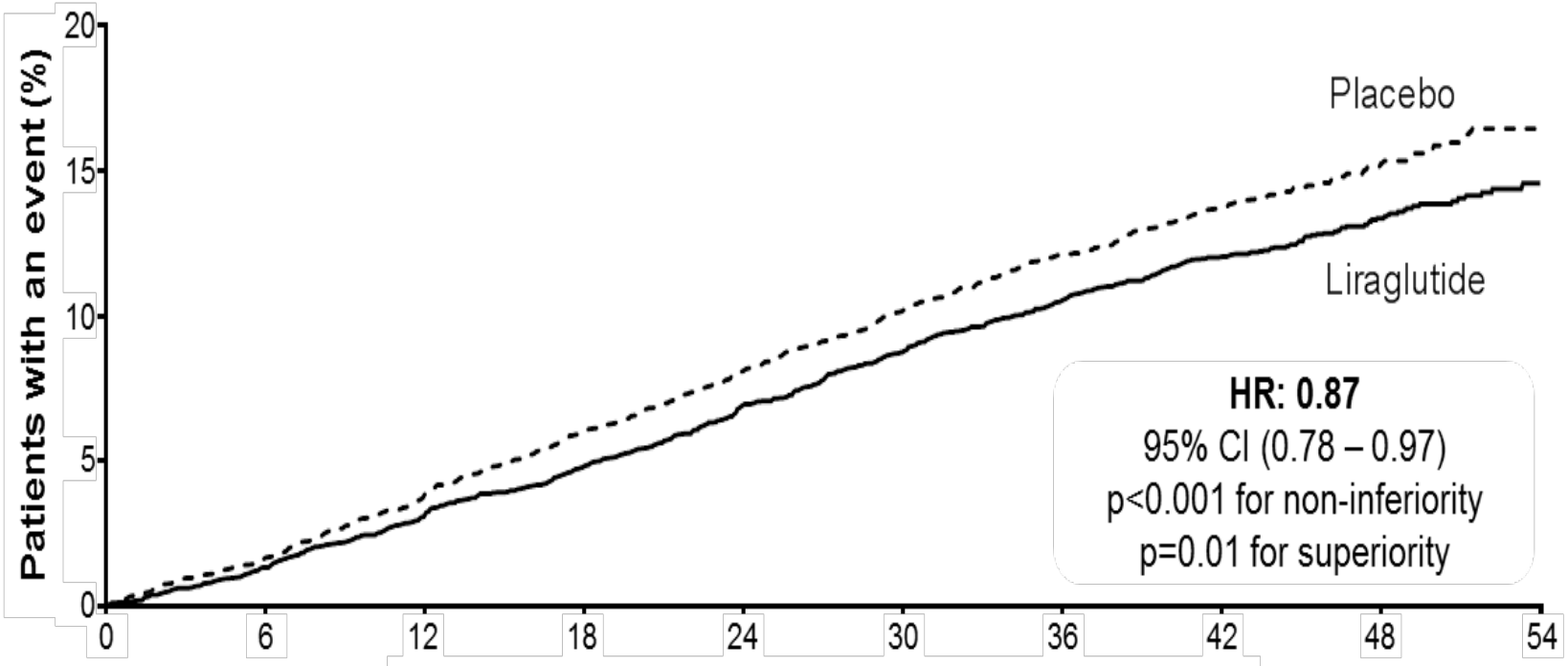
gliflozins reduce CV deaths

(EMPAREG secondary endpoint)



Zinman B et al.: NEJM 373:2117, 2015

LEADER: Primary outcome (MACE)
CV death, non-fatal MI, or non-fatal stroke



Patients at risk

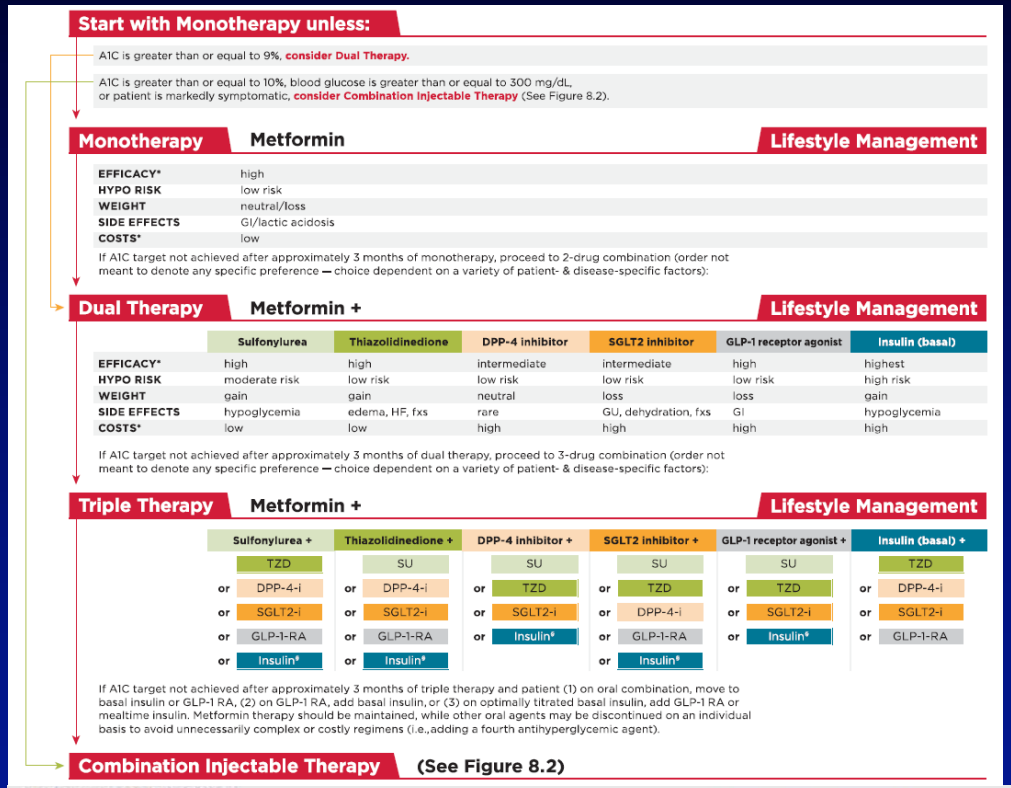
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Marso SP et al.: NEJM 375:311, 2016

ADA Standards of Medical Care in Diabetes

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES (p: S65-S71)
CV DISEASE AND RISK MANAGEMENT (p: S84)



Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy Metformin **Lifestyle Management**

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy Metformin + **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy Metformin + **Lifestyle Management**

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin‡	or GLP-1-RA	or Insulin‡	or GLP-1-RA
or Insulin‡	or Insulin‡		or Insulin‡		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e.,adding a fourth antihyperglycemic agent).

Combination Injectable Therapy **(See Figure 8.2)**

EMPA-REG OUTCOME Study

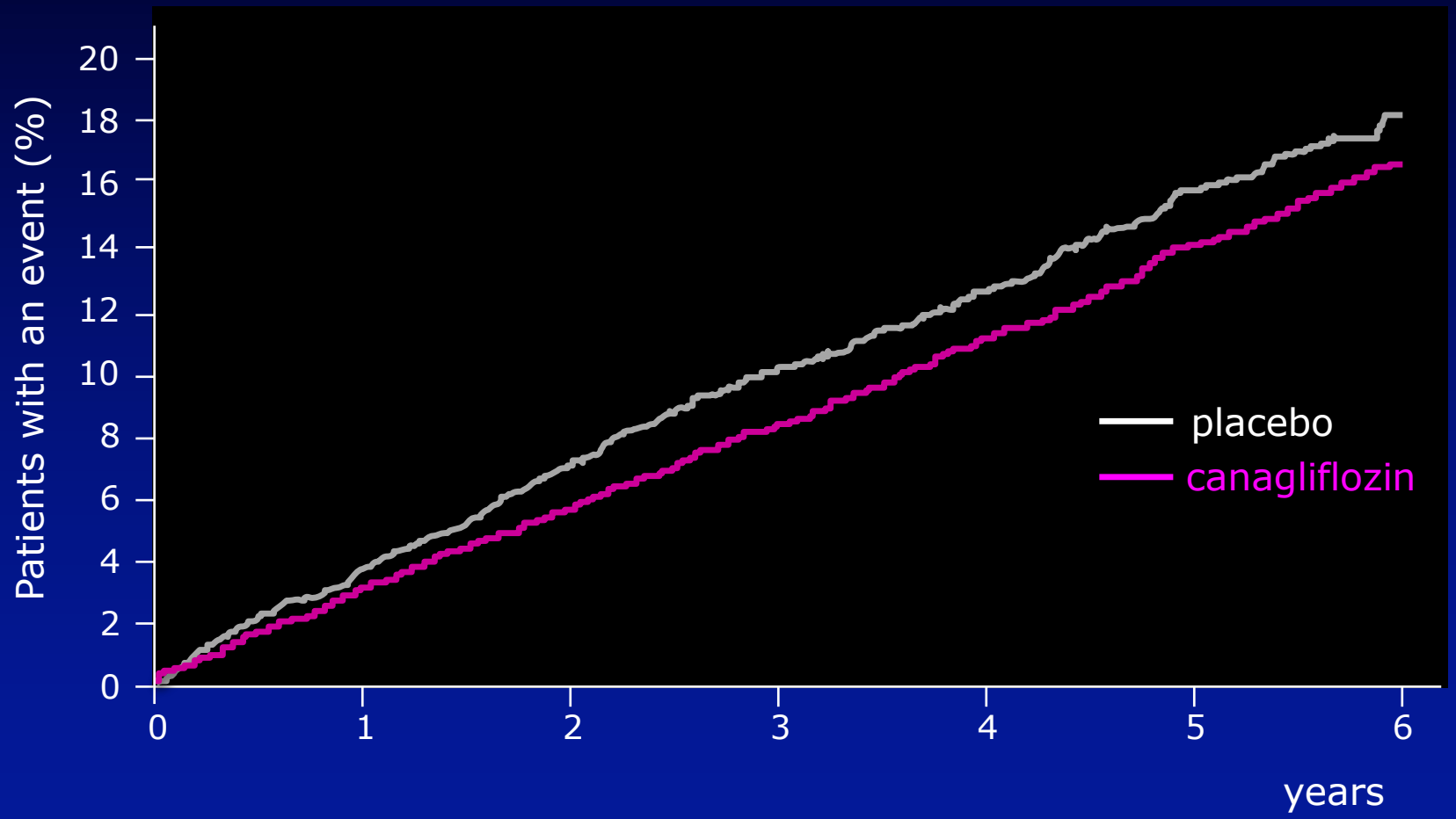
The BI10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, a SGLT2 inhibitor, versus placebo and standard care, on cardiovascular outcomes in patients with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI,
stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group) and cardiovascular death by 38%(absolute rate 3.7% vs. 5.9%) (29). The FDA recently added a new indication for empagliflozin, to reduce the risk of cardiovascular death in adults with type 2 diabetes and cardiovascular disease. Whether other SGLT2 inhibitors will have the same effect in high-risk patients and whether empagliflozin or other SGLT2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• Rare hypoglycemia • ↓ Weight • ↓ Blood pressure • Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High

CANVAS

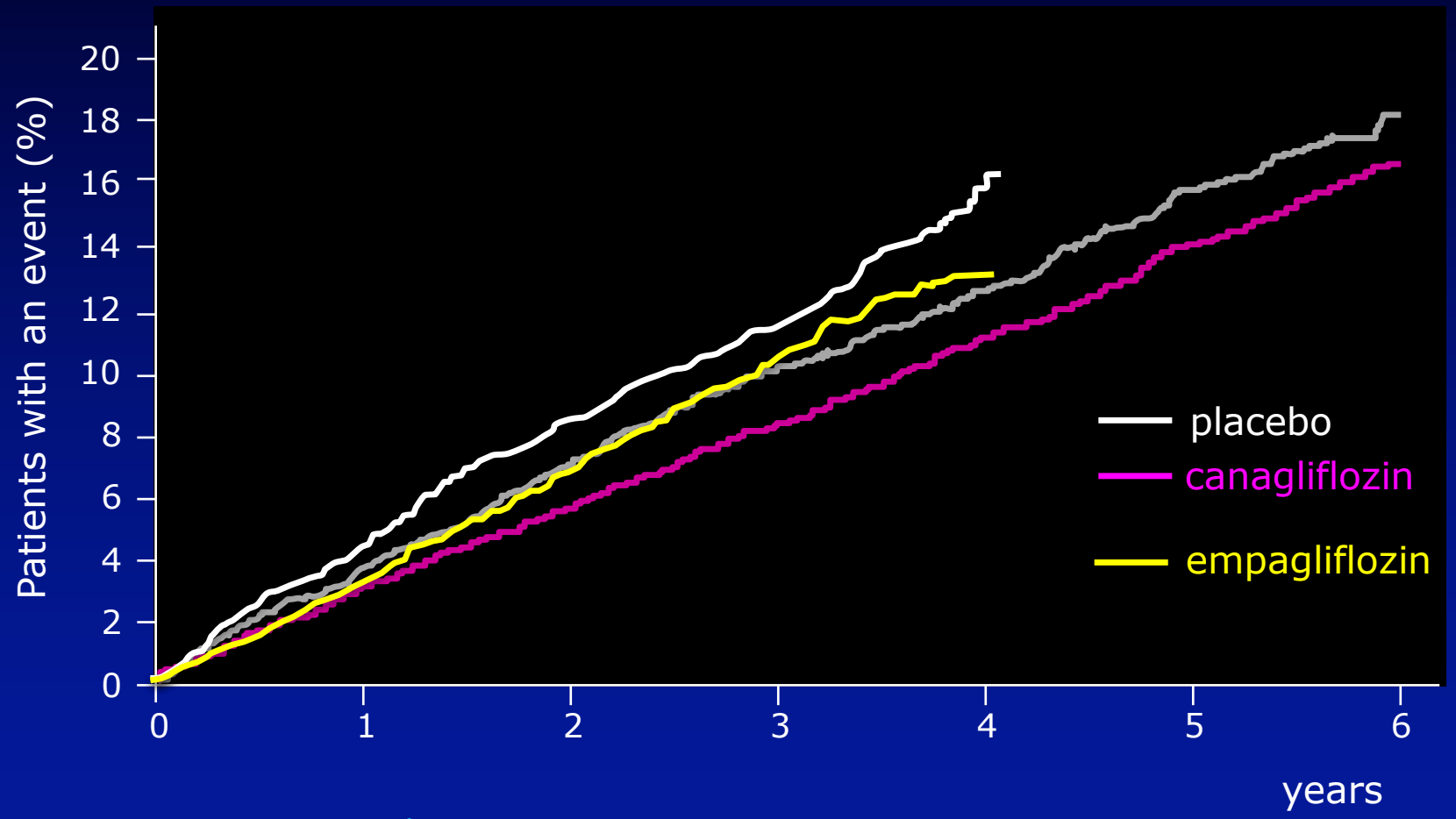
primary MACE outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



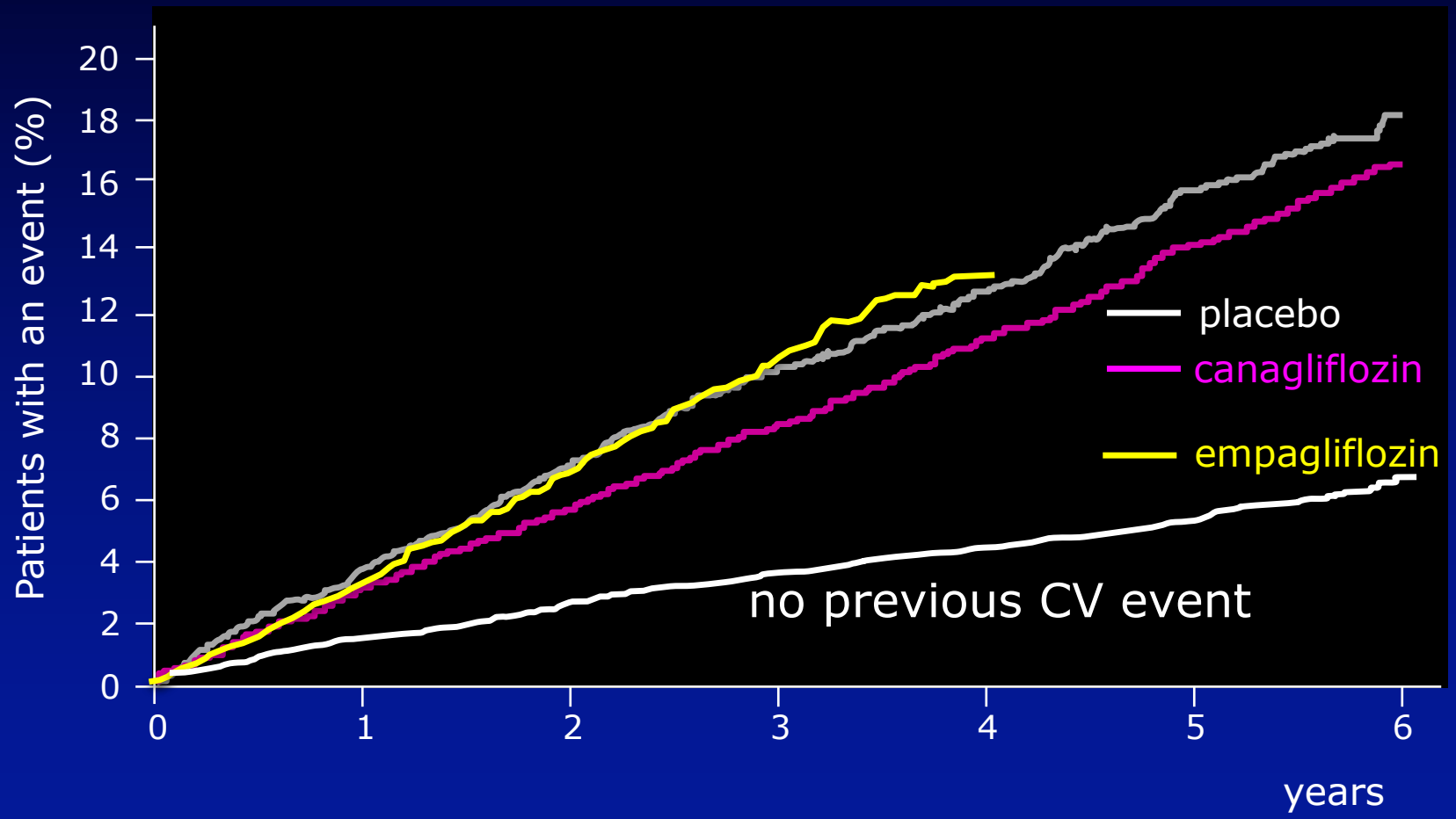
EMPAREG, Zinman B et al.: NEJM 373:2117, 2015
CANVAS, Neal B et al.: NEJM Jun 12, 2017

CANVAS & EMPAREG
primary MACE outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



EMPAREG, Zinman B et al.: NEJM 373:2117, 2015
CANVAS, Neal B et al.: NEJM Jun 12, 2017

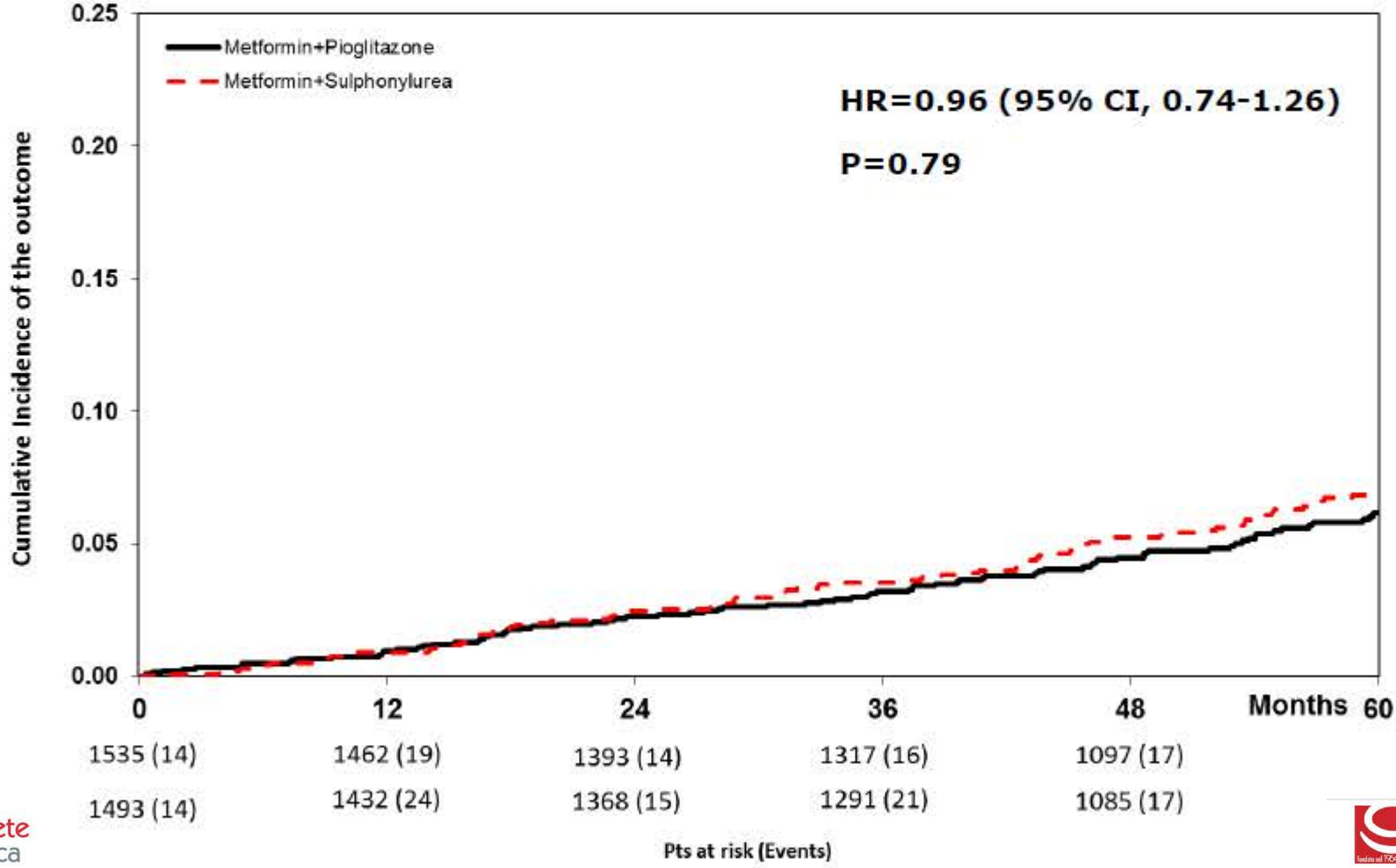
CANVAS & EMPAREG
primary MACE outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



EMPAREG, Zinman B et al.: NEJM 373:2117, 2015
CANVAS, Neal B et al.: NEJM Jun 12, 2017

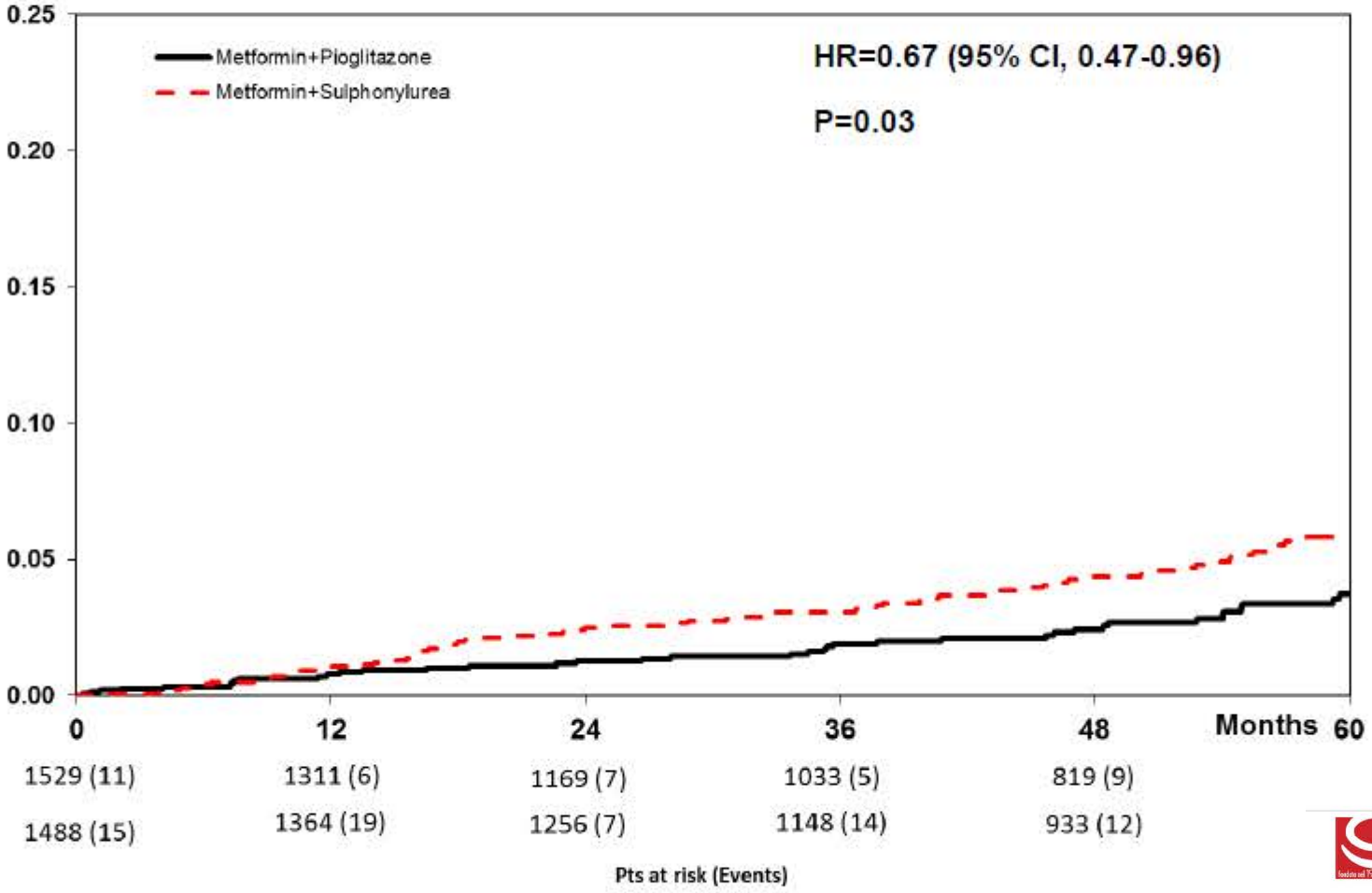
Primary outcome

All-cause death, non-fatal MI - including silent MI, non-fatal stroke, urgent coronary revascularization



Key secondary outcome, on treatment population

Sudden death, fatal and non-fatal MI (including silent MI), fatal and non-fatal stroke, major leg amputation (above the ankle), coronary, leg or carotid arteries revascularization



CVD-REAL: Health Records

Truven MarketScan Claims & Encounters and linked Medicare

National full-population registries

National full-population registries

National full-population registries

Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN)

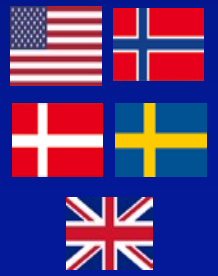
Diabetes Patienten Verlaufsdokumentation (DPV) initiative

cohort 1
HHF

cohort 2

all cause death

composite HHF + all cause death



Kosiborod M. et al.: 66th ACC Washington DC, 2017

propensity match

SGLT-2i

search a
patient similar
for 42 different
criteria

other glucose lowering drugs

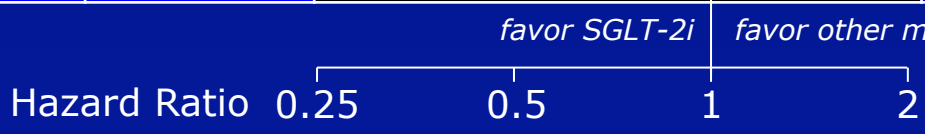
other glucose
lowering drugs

compared 1:1

CVD-REAL: all cause death

primary analysis (N=215,622)

database	N	events	HR (95%CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1,15)
Total	215,622	1334	0.49 (0.41, 0.57)



CVDREAL

Kosiborod M. et al.: 66th ACC Washington DC, 2017

in conclusione …

- in prevenzione secondaria alcuni farmaci sono efficaci nel ridurre eventi CV.
- non è (né sarà mai) possibile stabilire differenze in prevenzione primaria.
- i risultati in prevenzione secondaria sono estrapolabili alla primaria?