Managing T2DM and CVD
Exploring New Evidence and Opportunities

Darshi Sunderam, MD

Chief of Endocrinology

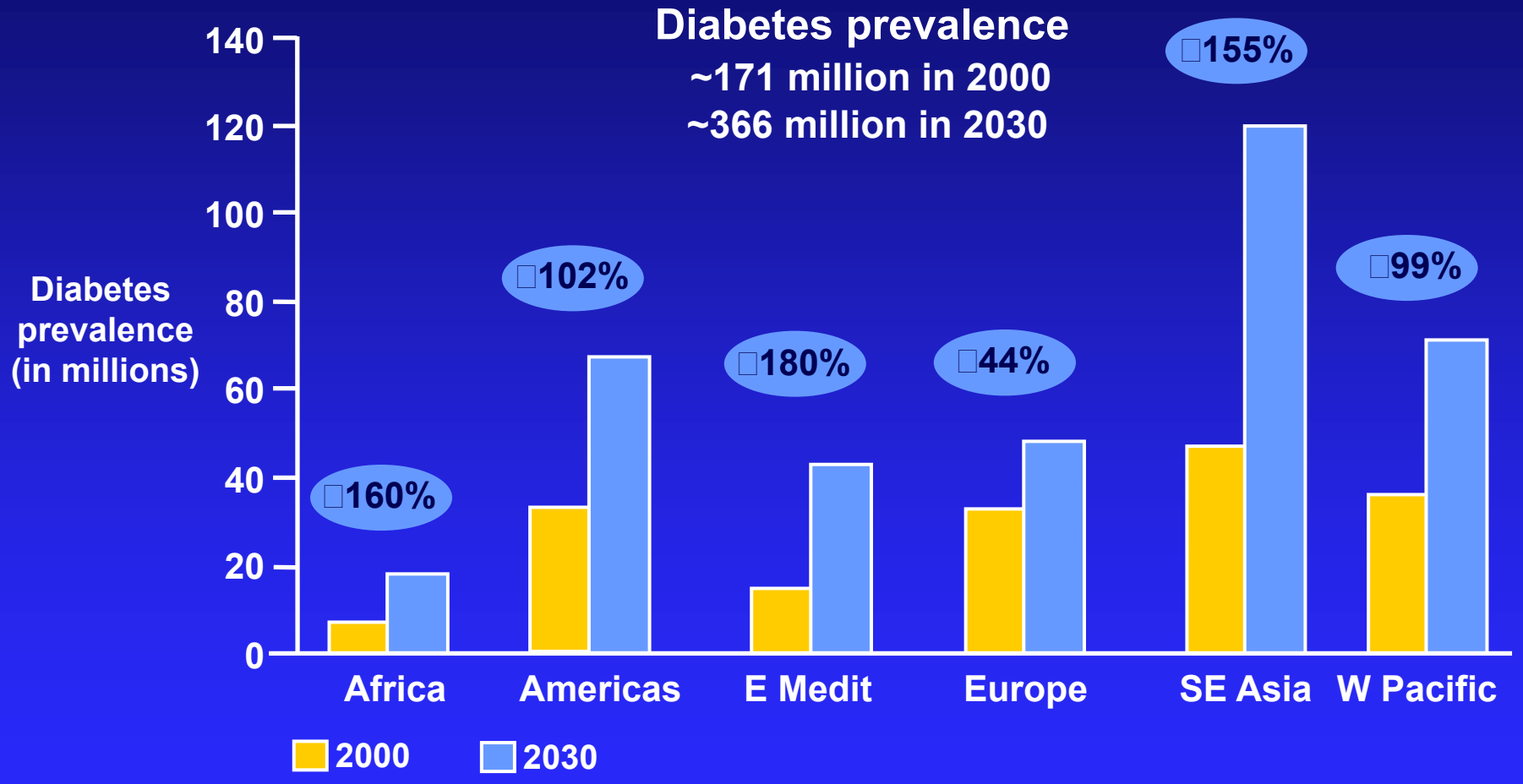
East Orange General Hospital

Objectives

- Pathophysiology and disease progression
- Glycemia and CVE
- Glycemic control
  - Intensive vs conservative
  - Early vs late
- CV outcome trials

Worldwide Prevalence of Diabetes:

Expected to Increase

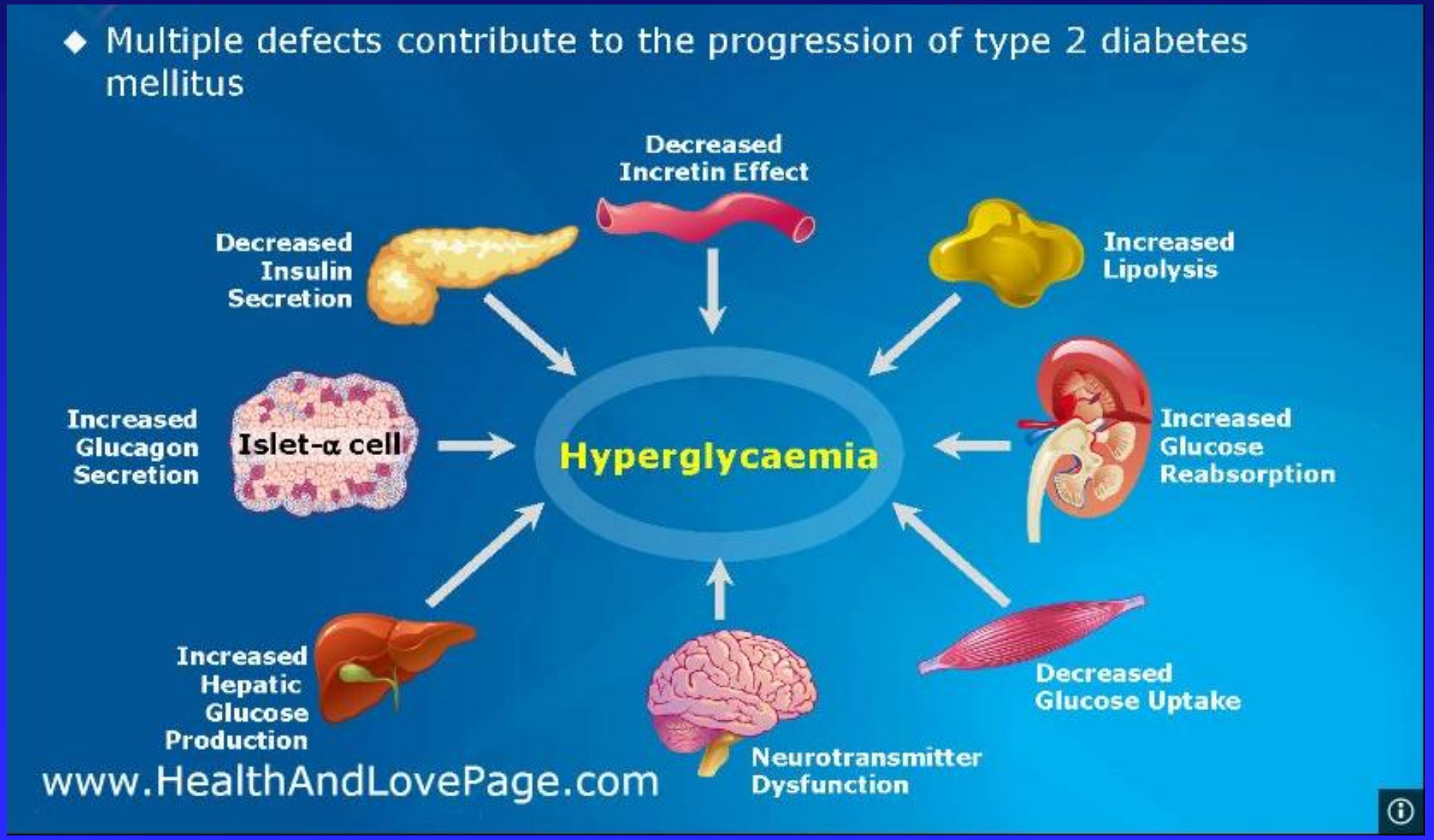


World Health Organization. www.who.org.

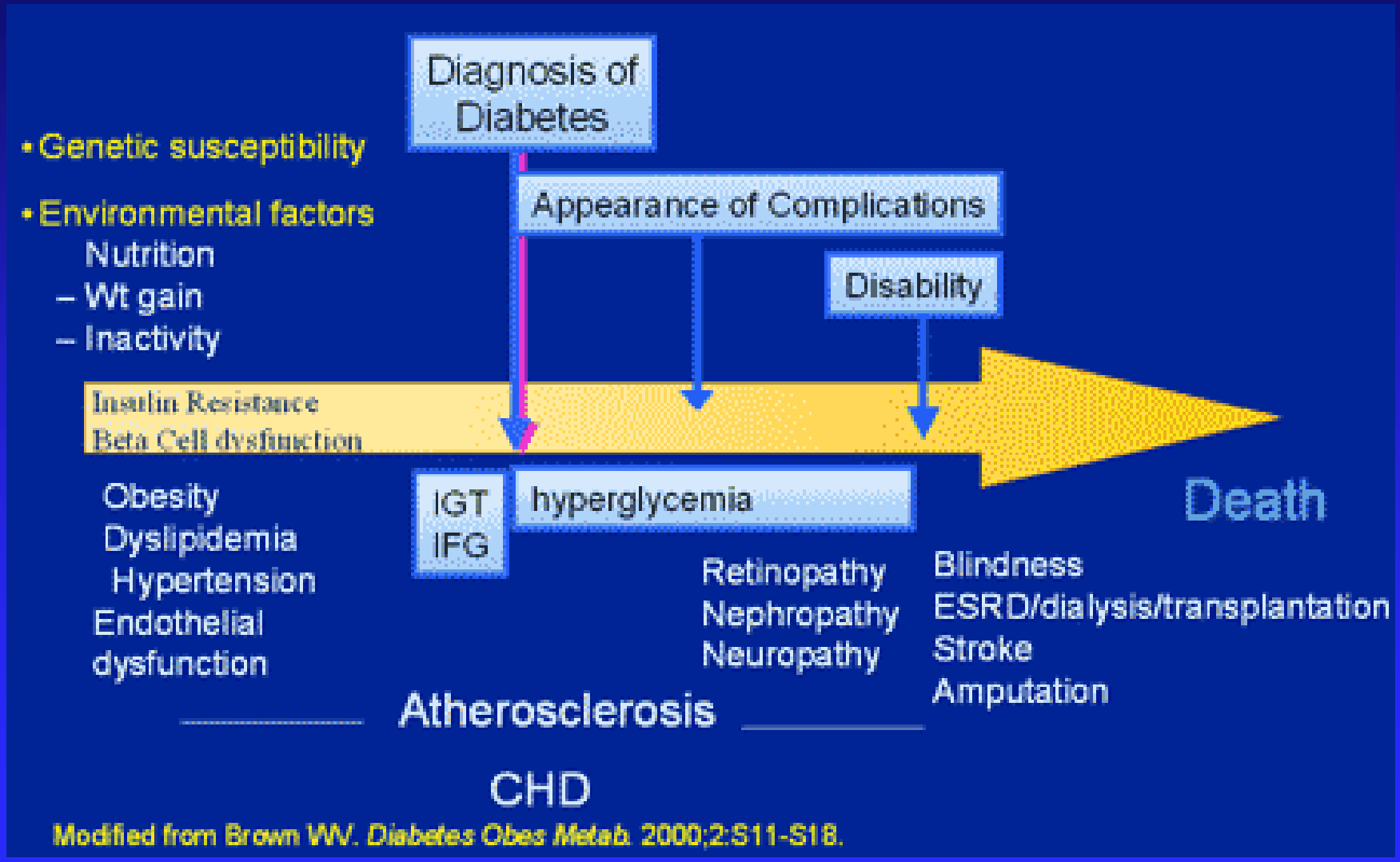
Pathophysiology and Disease Progression

Pathogenesis of T2DM:

The Ominous Octet

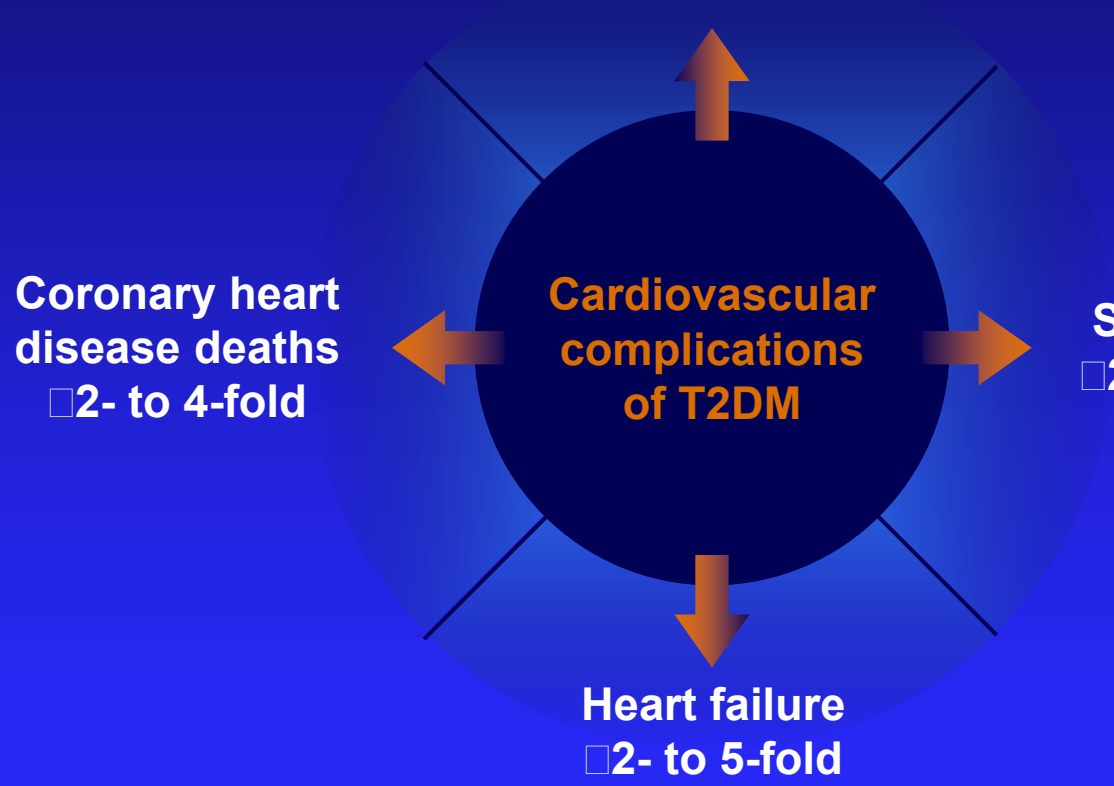


Progression of T2DM



Cardiovascular Disease and Diabetes

~65% of deaths are due to CV disease



Coronary heart disease deaths
2- to 4-fold

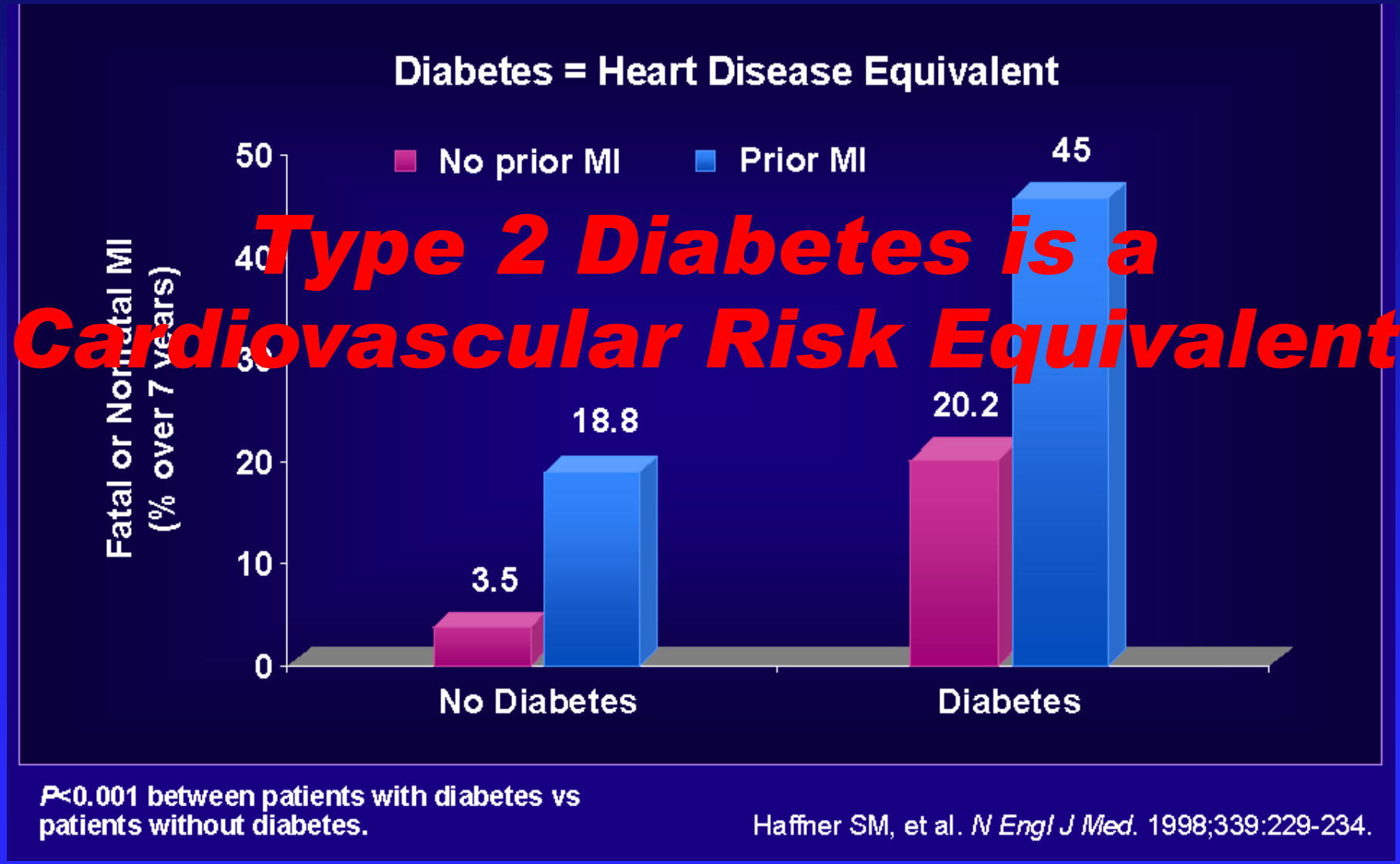
Stroke risk
2- to 4-fold

Heart failure
2- to 5-fold

T2DM = type 2 diabetes mellitus

Bell DSH. *Diabetes Care*. 2003;26:2433-41.
Centers for Disease Control (CDC). www.cdc.gov.

Incidence of Fatal or Nonfatal MI With or Without T2DM

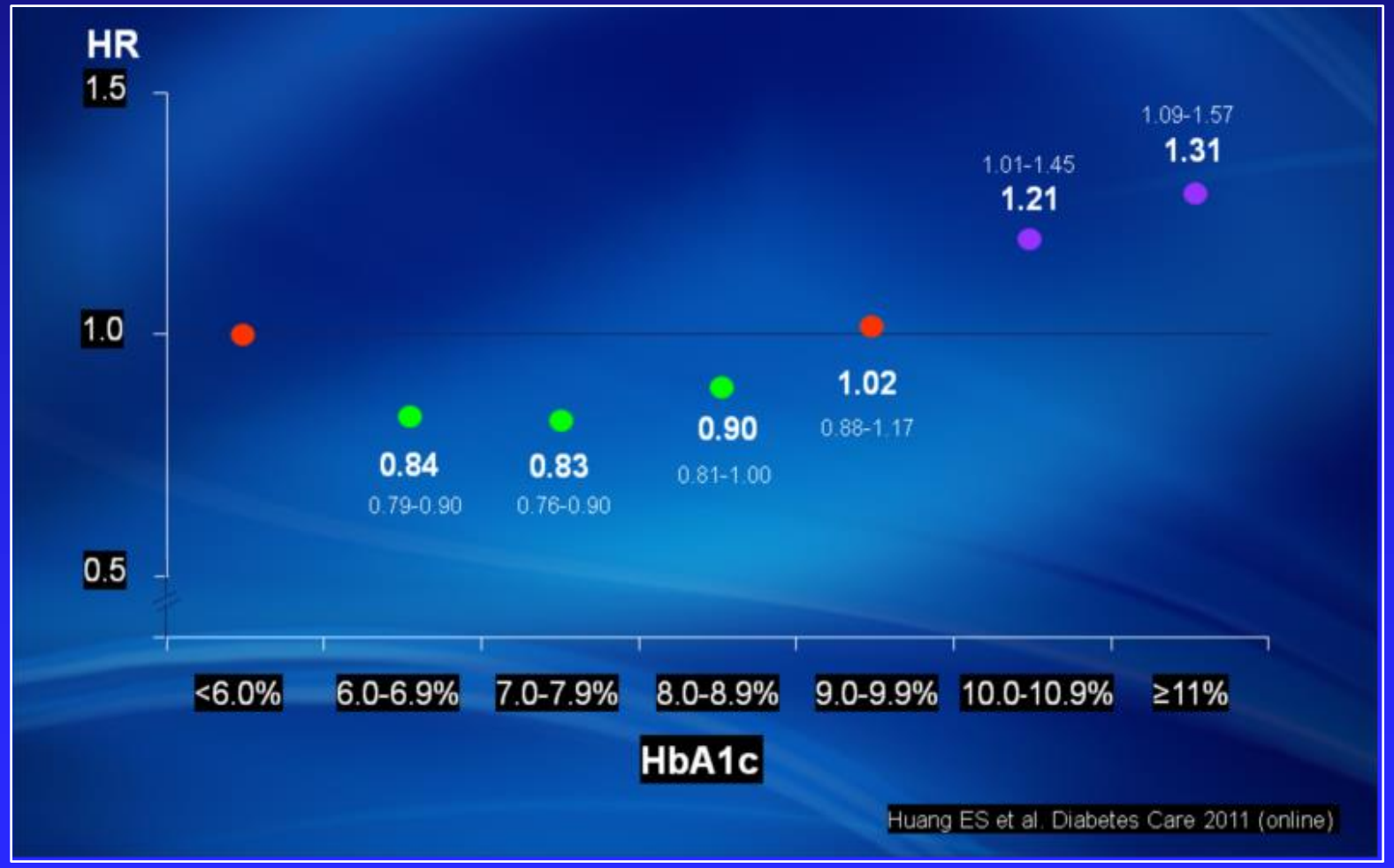


P<0.001 between patients with diabetes vs patients without diabetes.

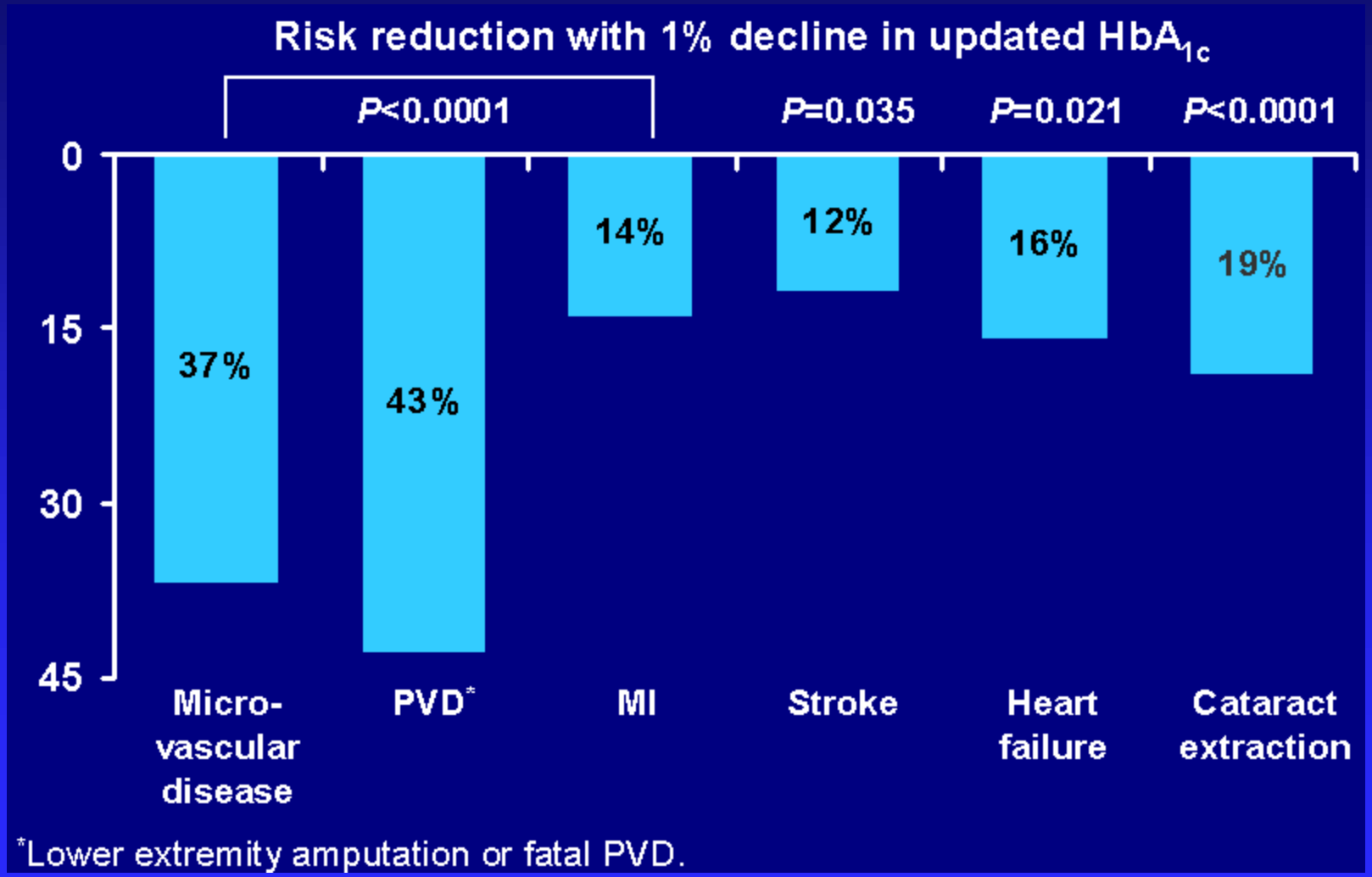
Haffner SM, et al. *N Engl J Med.* 1998;339:229-234.

Mortality and A1c in T2DM:

Kaiser-Permanente Cohort



UKPDS: Risk Reduction in Diabetes-Related Complications

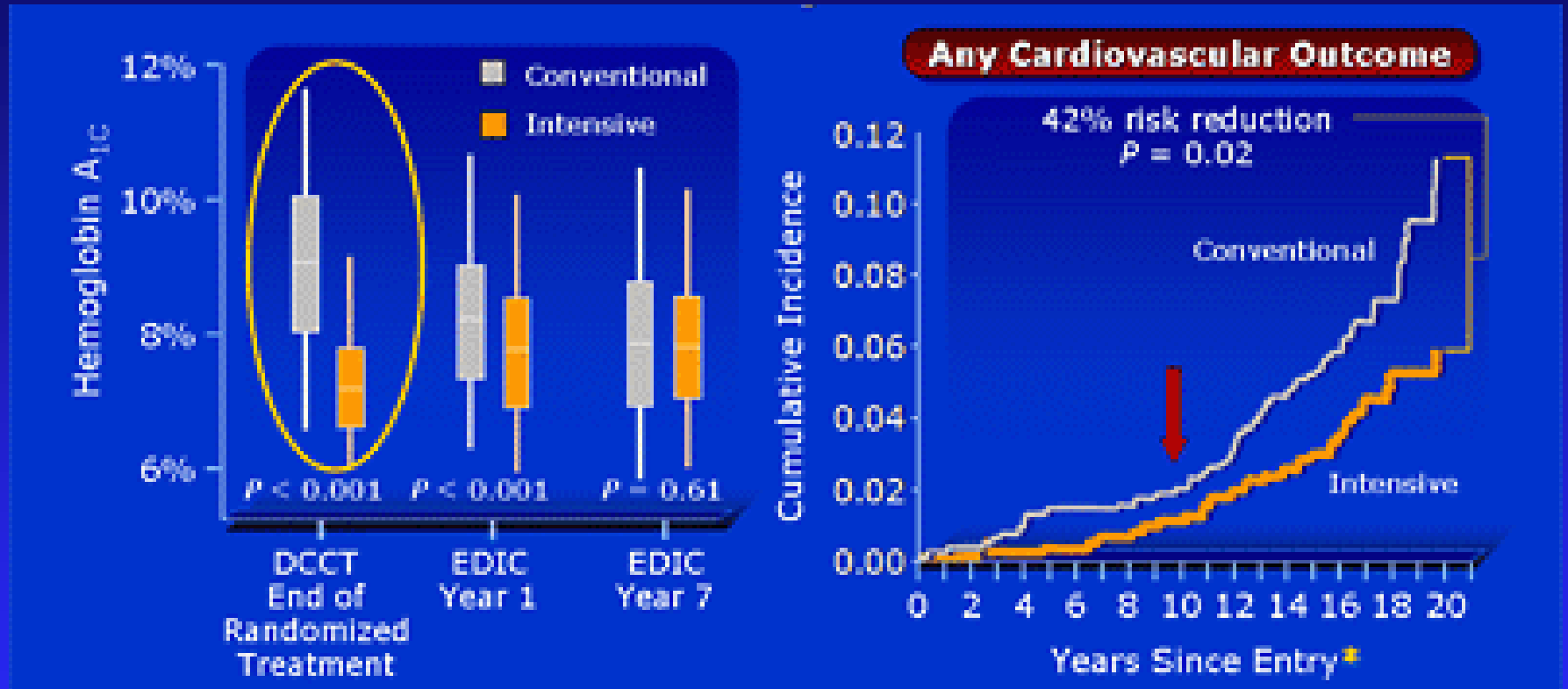


Stratton IM et al. BMJ. 2000; 321: 405-412.

UKPDS 80: "Legacy" Effect of Intensive Glucose Control on MI

Early Intensive Glycemic Control Reduces CVE

DCCT-EDIC: Long-Term Risk of Macrovascular Complications



*Diabetes Control and Complications Trial (DCCT) ended and Epidemiology of Diabetes Interventions and Complications (EDIC) began in year 10 (1993). Mean follow-up: 17 years.

Intensive Glycemic Control
Controversial Results!
WHY?

Early vs Late Intervention in Type 2 Diabetes

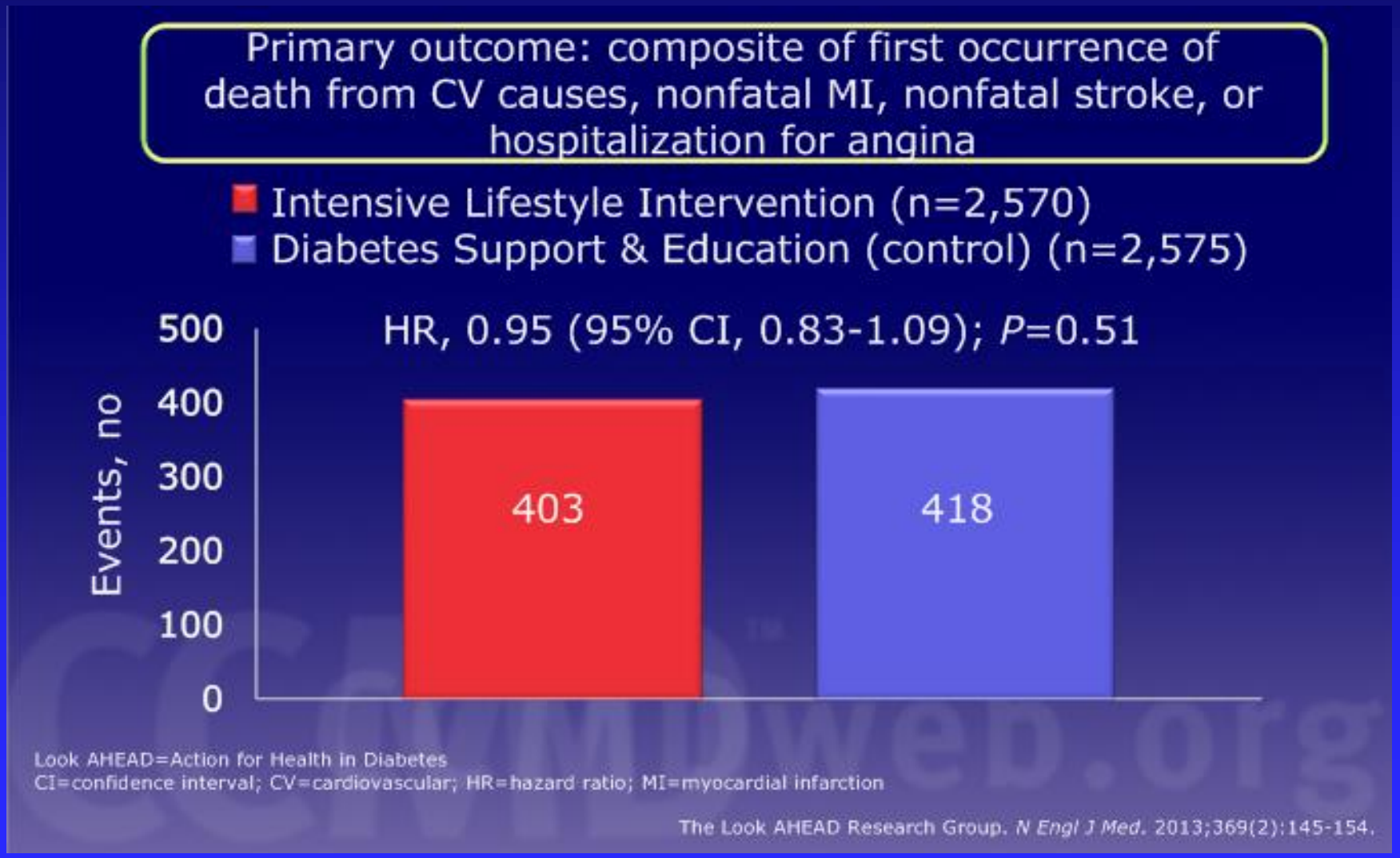
Trial	Intensive Arm HbA_{1c} Reduction	No Patients / Trial Duration	Disease Severity	Macrovascular Benefit
A				
A				
V				
U				

"One Size Fits All" may not be the best glucose-lowering strategy

ACC
2008;359:1577-1589.

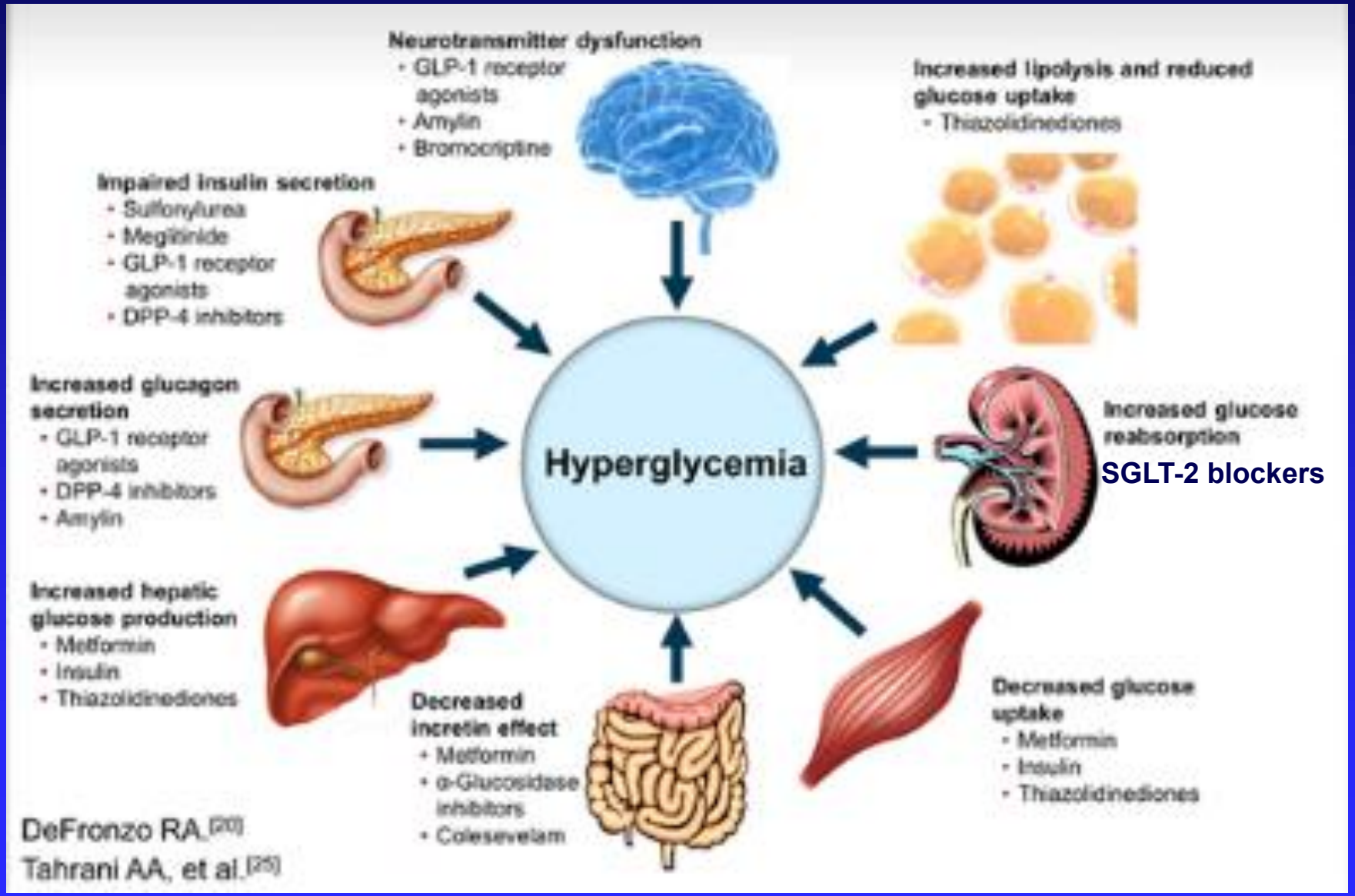
Does Intensive Lifestyle Intervention Have an Effect on CV Outcomes?

Look AHEAD: No Reduction in CV Events with Lifestyle Changes



CVD-Risk Specific To Anti-hyperglycemic Agents

Hyperglycemia in Type 2 Diabetes



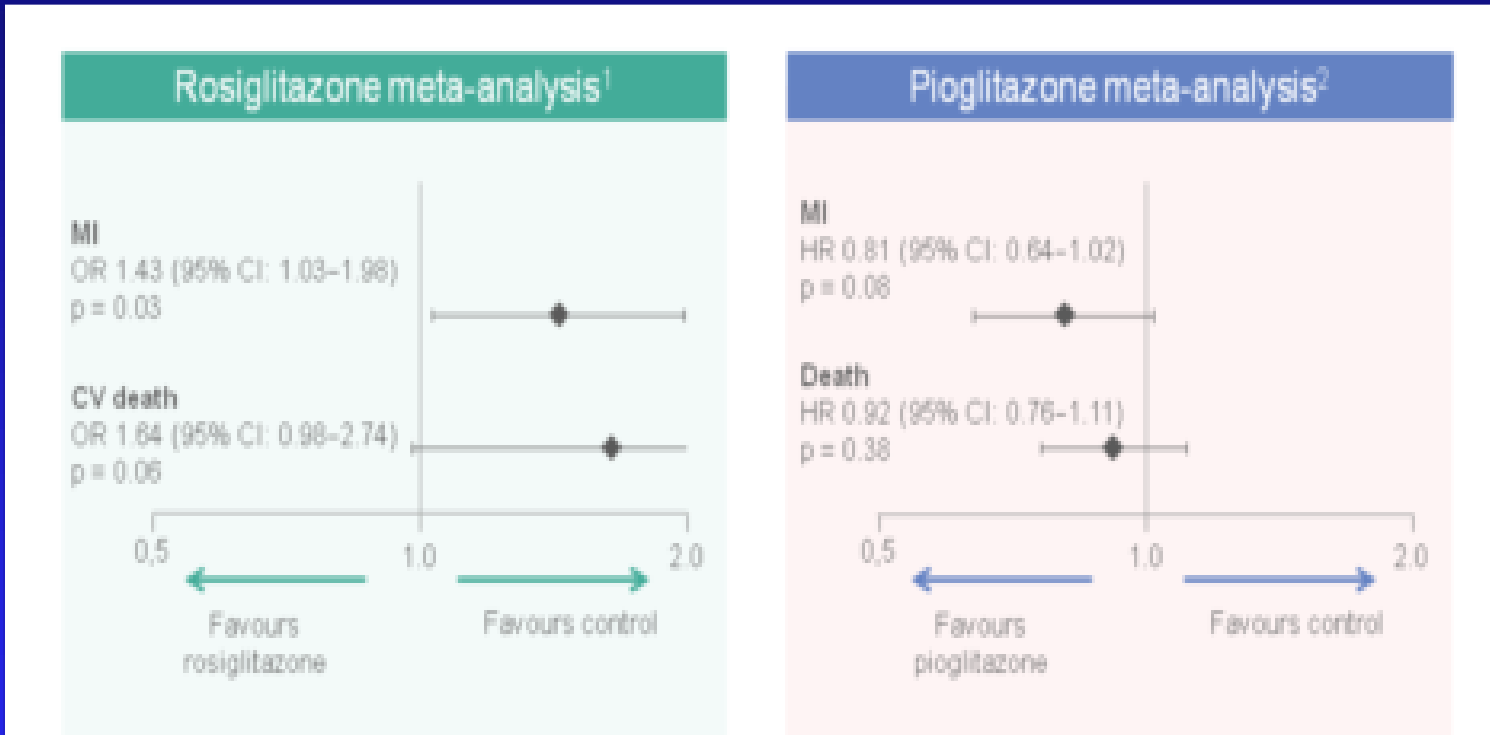
Meta-analysis of SU CV Safety Trials Found No Consistent Association with MACE Risk

CV safety of SUs cannot be considered established unless evaluated in long-term CVOTs

UKPDS 34 Provides Some Evidence for Beneficial CV Effects of Metformin in Overweight Patients

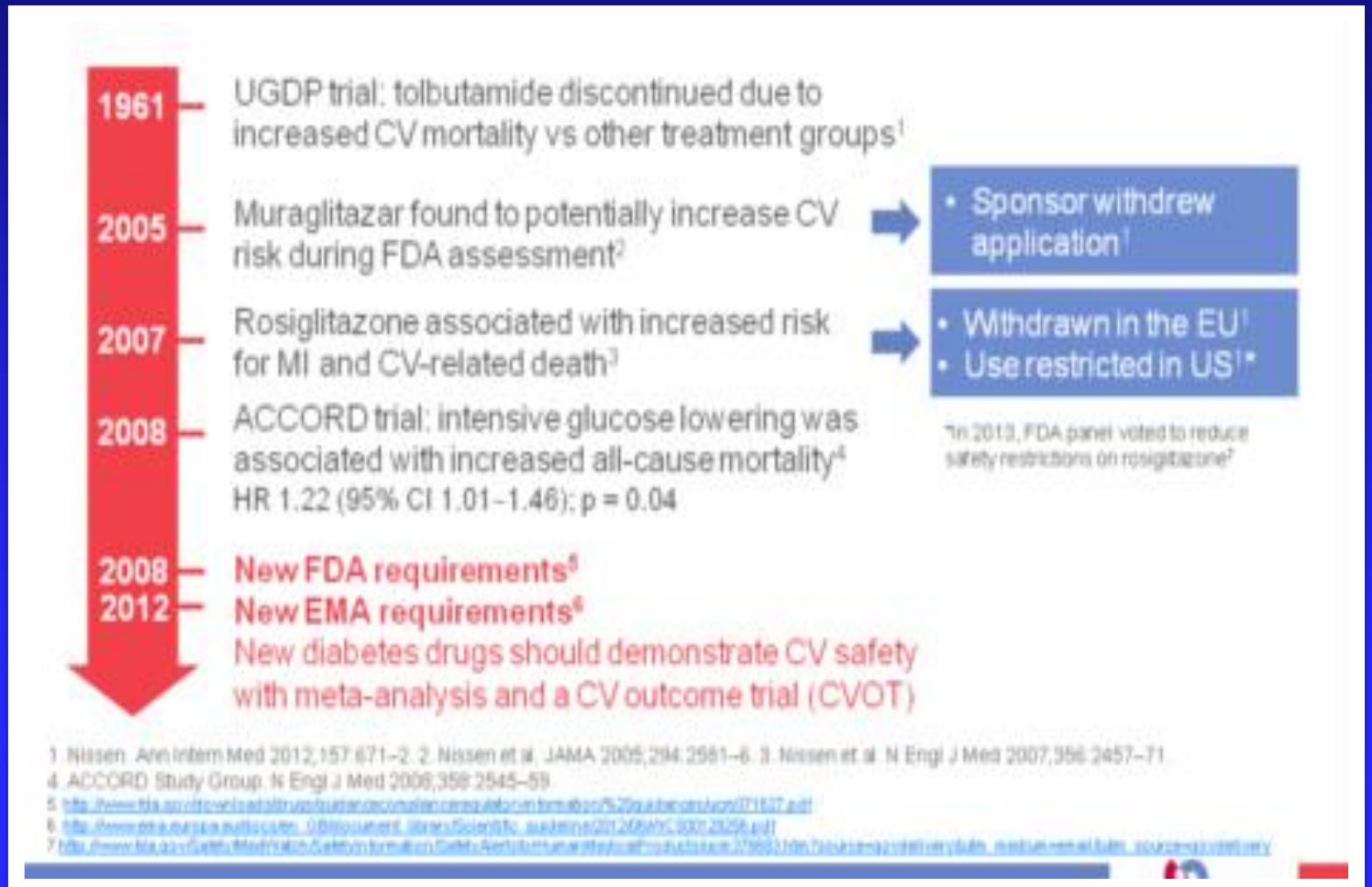
There remains a paucity of evidence from large, long-term placebo-controlled CV outcome trials.

Separate Meta-analysis Suggested Differing CV Effects of Drugs within the TZD Class

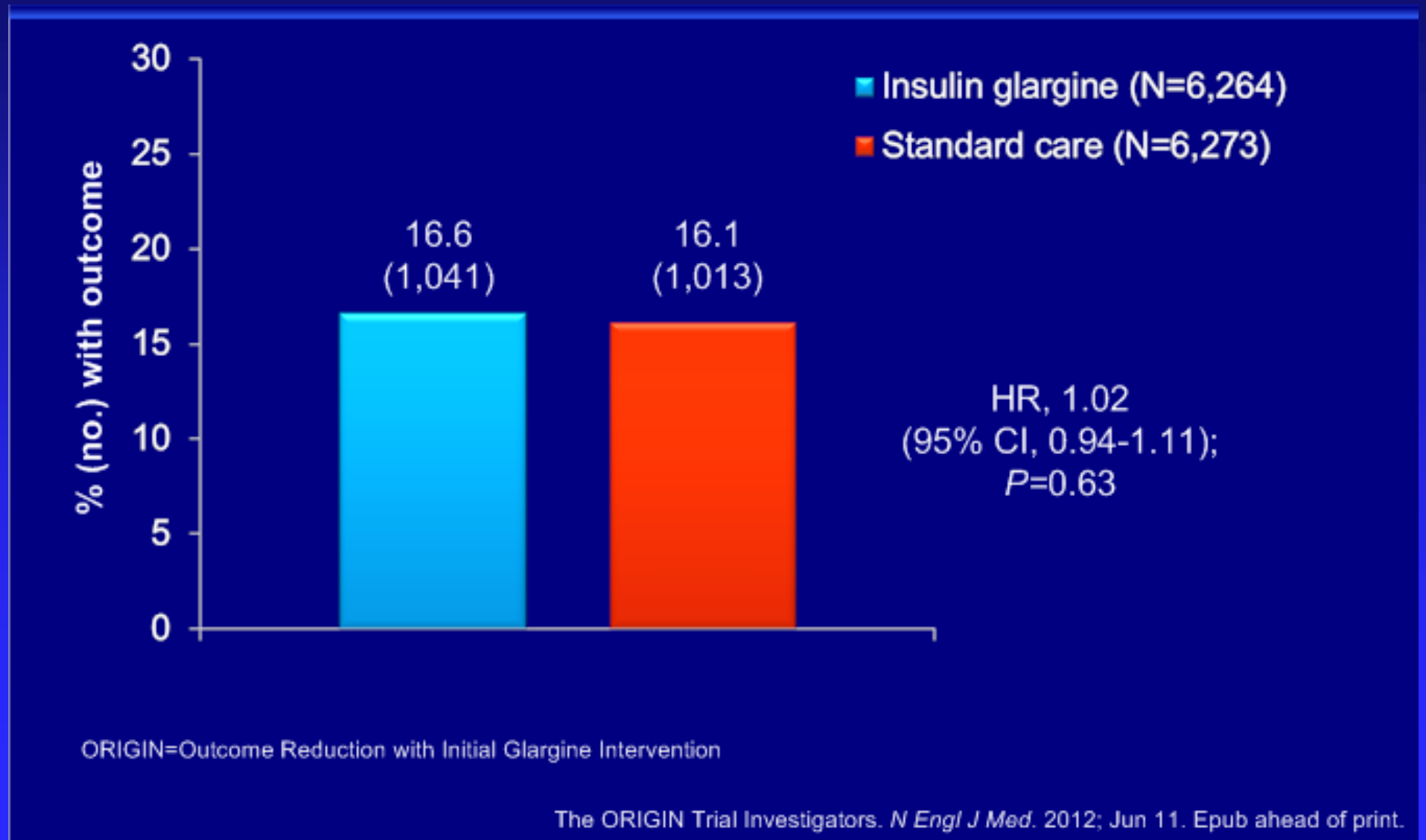


No clinical trial directly compares the CV effects of pioglitazone and rosiglitazone

Adverse CV Events Led the FDA to Require Demonstration of CV Safety for New Glucose-lowering Drugs



Origin Glargine Trial



ORIGIN=Outcome Reduction with Initial Glargine Intervention

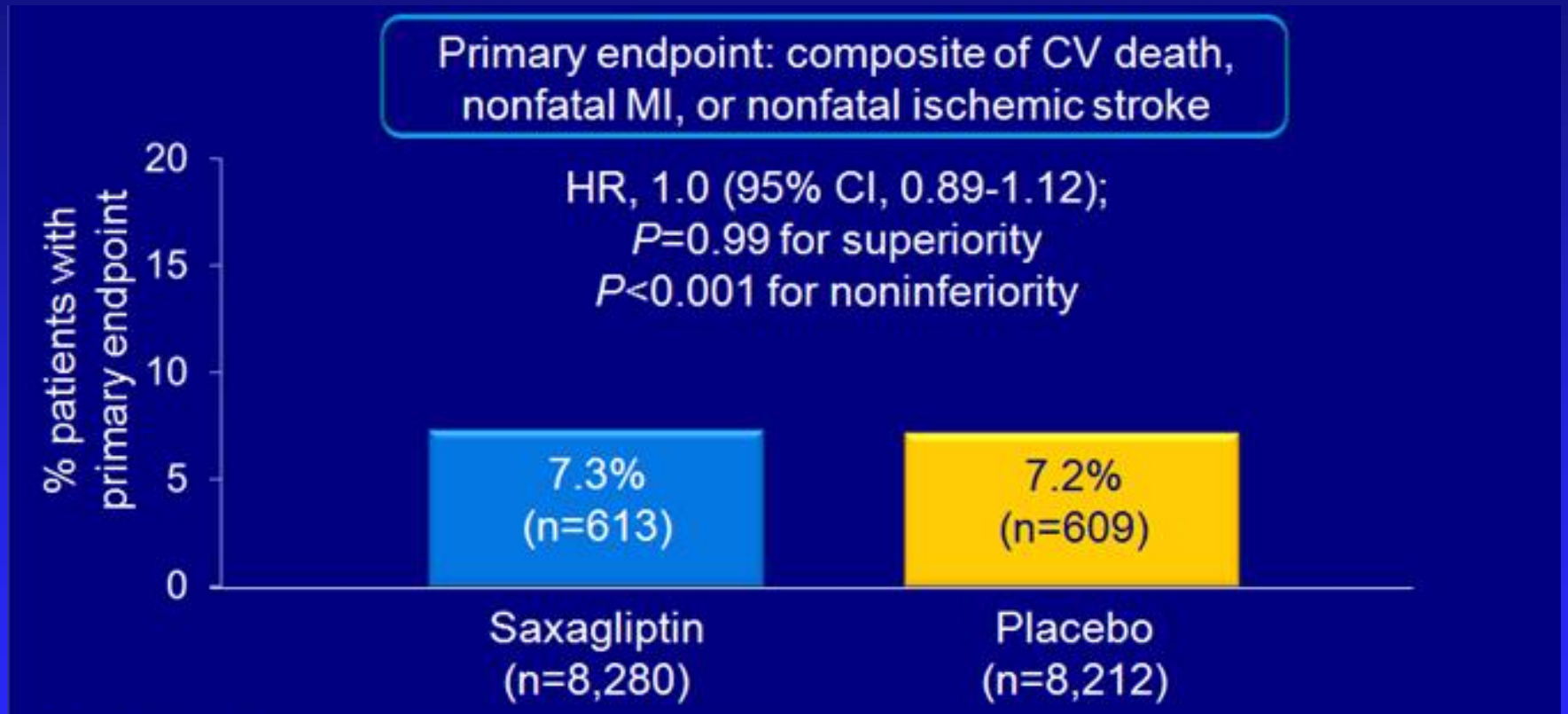
The ORIGIN Trial Investigators. *N Engl J Med*. 2012; Jun 11. Epub ahead of print.

Ongoing Cardiovascular Outcome Trials: DPP-4 Inhibitors

	Therapies	#	Population	Endpoints	Results
DPP-4 Inhibitors					
TECOS	Sitagliptin/ Placebo	14,000	Established CVD	CV death, NF MI or stroke, hosp for UA	Dec 2014
EXAMINE	Alogliptin/ Placebo	5400	ACS 15-90 days before	CV death, NF MI or stroke	Dec 2014
SAVOR-TIMI 53	Saxagliptin/ Placebo	16,500[3]	CVD or ≥ 2 RF	CV death, NF MI or ischemic stroke	Apr 2014
CAROLINA	Linagliptin/ Glimepiride	6000	CVD or ≥ 2 RF	CV death, NF MI or stroke, hosp for UA	Sept 2018

Adapted from: 1-Golden SH. Am J Cardiol 2011;108 (Suppl):59B-67B; 2-Fonseca V. Am J Cardiol 2011;108 (supp):52B–58B; 3- Clinicaltrials.gov

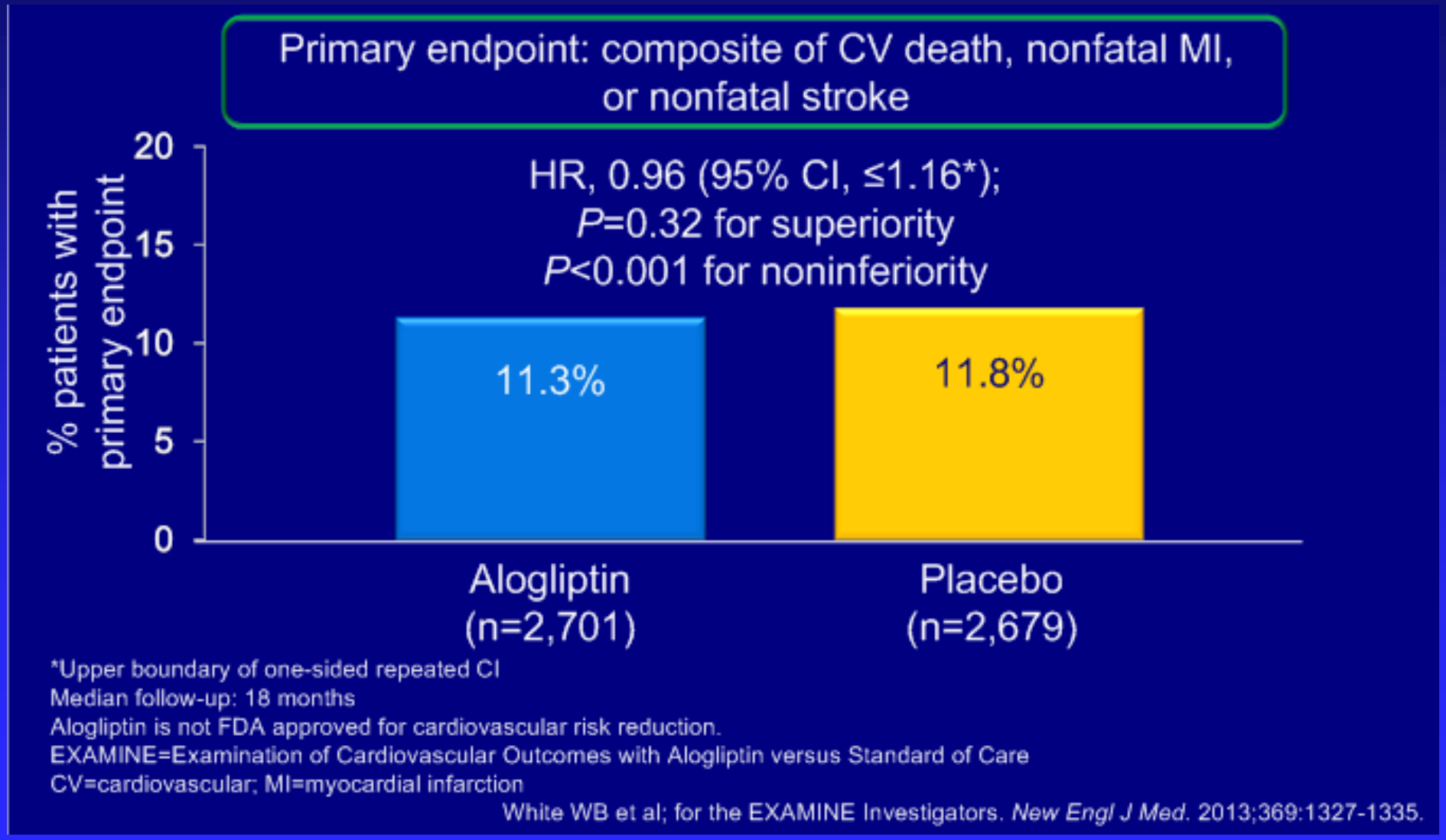
SAVOR TIMI 53: No Increase in CV Events with Saxagliptin in Patients with or At-risk for CVD



Saxagliptin is not FDA approved for cardiovascular risk reduction.
SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; CV=cardiovascular; MI=myocardial infarction

Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. *New Engl J Med.* 2013. DOI:10.1056/NEJMoa1307684.

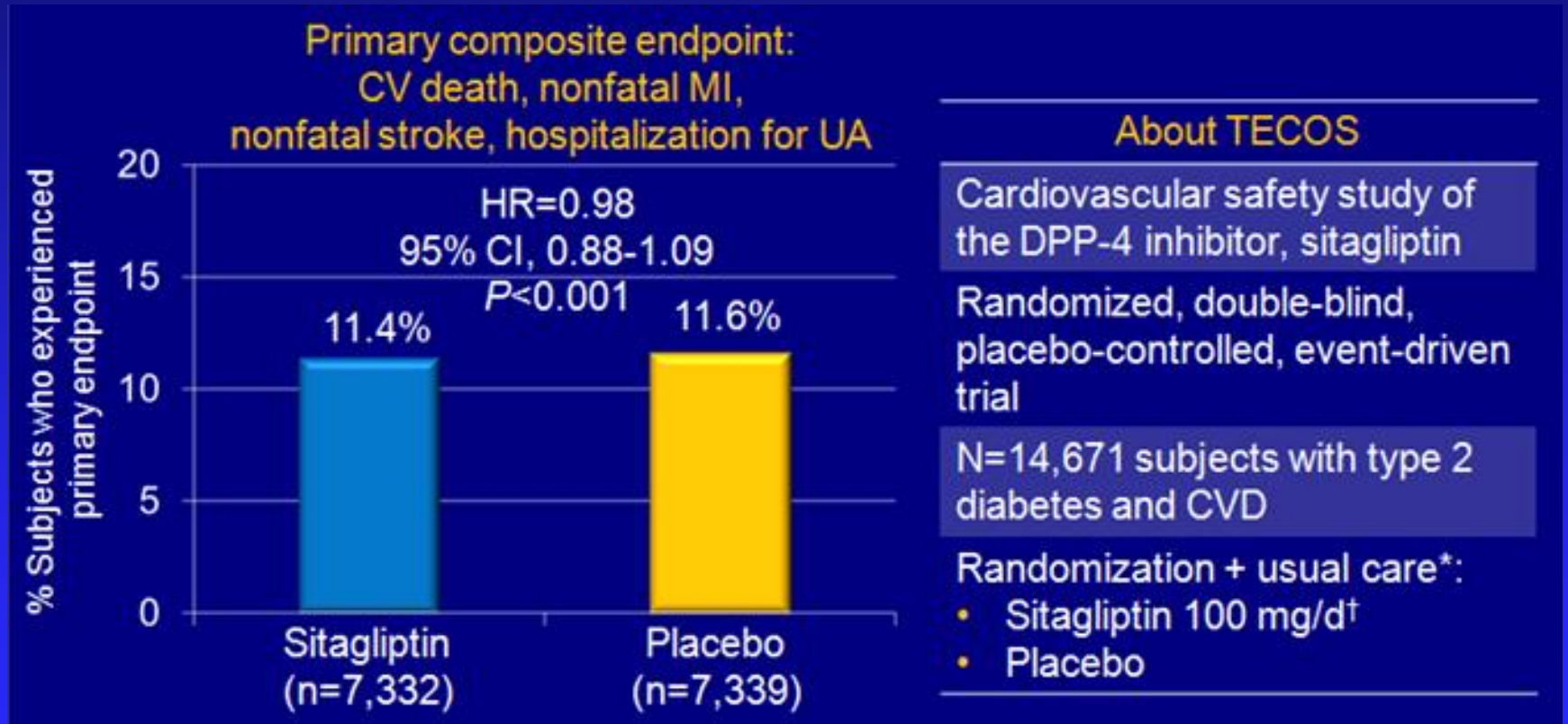
EXAMINE: No Increase in CV Events with Alogliptin Primary Endpoint



*Upper boundary of one-sided repeated CI
Median follow-up: 18 months
Alogliptin is not FDA approved for cardiovascular risk reduction.
EXAMINE=Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care
CV=cardiovascular; MI=myocardial infarction

White WB et al; for the EXAMINE Investigators. *New Engl J Med*. 2013;369:1327-1335.

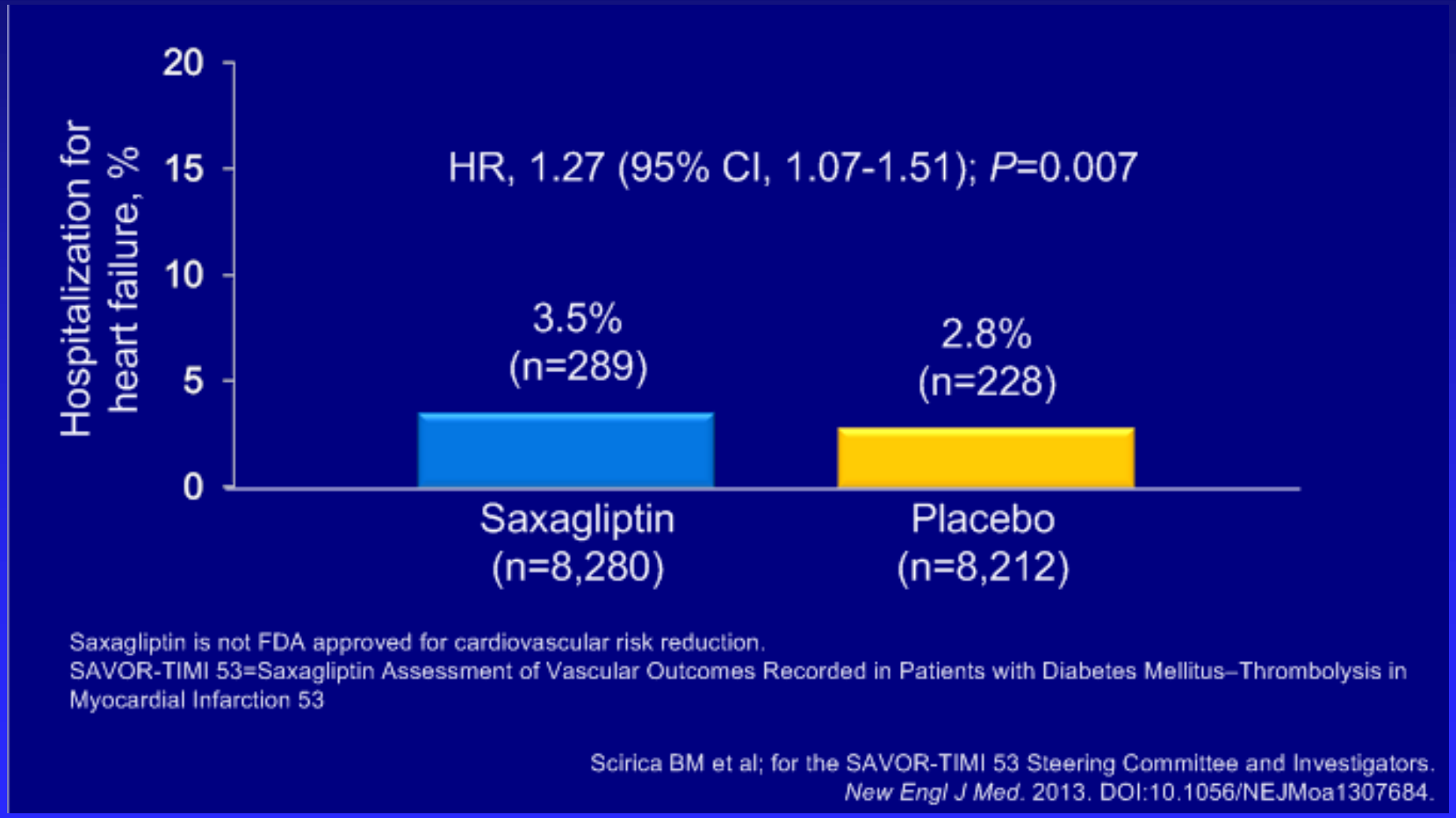
TECOS: No Increased CV Risk with Sitagliptin vs Placebo in High Risk Subjects with Type 2 DM



TECOS=Trial Evaluating Cardiovascular Outcomes with Sitagliptin
HR=hazard ratio; UA=unstable angina
*Or 50 mg/d if baseline eGFR ≥30 and <50 ml/min/1.73 m^2; †Stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin)

Green JB, et al. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1501352.

SAVOR-TIMI 53: Saxagliptin Increased Hospitalization for Heart Failure



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SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53

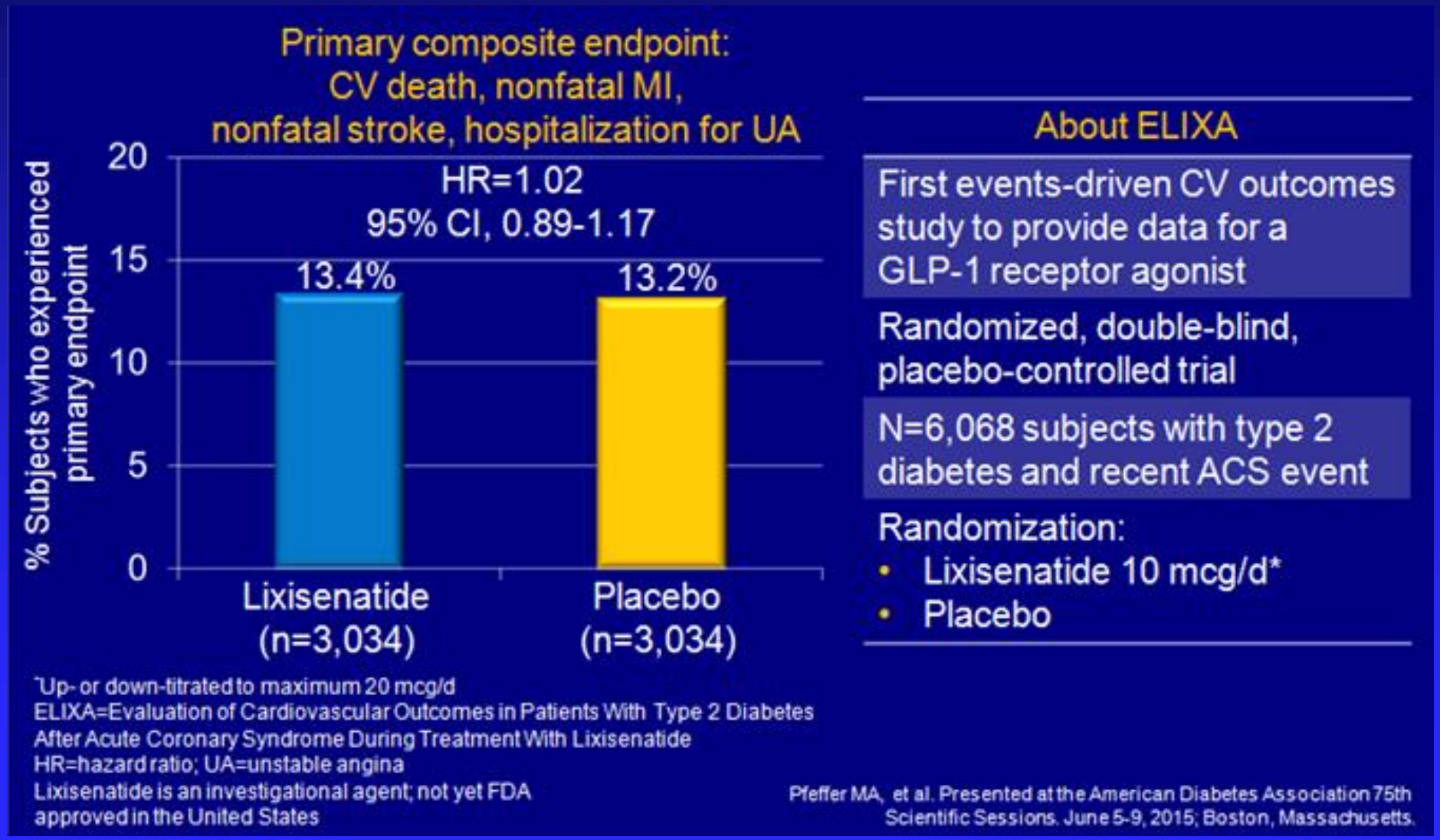
Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. *New Engl J Med*. 2013. DOI:10.1056/NEJMoa1307684.

Ongoing Cardiovascular Outcome Trials: GLP-1 Agonists

	Therapies	#	Population	Endpoints	Results
GLP-1 agonists					
LEADER	Liraglutide/ Placebo	8754	CVD, PAD, CKD, CHF or RF if >60yrs	CV death, NF MI or stroke	Jan 2016
EXSCEL	Exenatide LAR/ Placebo	9500	Not specified	CV death, NF MI or stroke	Mar 2017
ELIXA	Lixisenatide/ Placebo	6000	ACS leading to hosp ≤180 days before	CV death, NF MI, NF stroke, hosp for UA	Oct 2013
REWIND	Dulaglutide/ Placebo	9622	CVD or ≥ 2 RF if age ≥ 60 years	CV death, NF MI, or NF stroke	Apr 2019

Adapted from: 1-Golden SH. Am J Cardiol 2011;108 (Suppl):59B-67B; 2-Fonseca V. Am J Cardiol 2011;108 (suppl):52B–58B; 3- Clinicaltrials.gov

ELIXA: No CV Risks or Benefits with Lixisenatide vs Placebo



EMPA-REG OUTCOME TRIAL

The first glucose-lowering agent to show CV benefit in an outcome trial.

EMPA-REG OUTCOME: Design and Baseline Characteristics

- CVOT for the SGLT2 inhibitor, empagliflozin
- 7,020 subjects with type 2 diabetes at high CV risk on standard care randomized to:

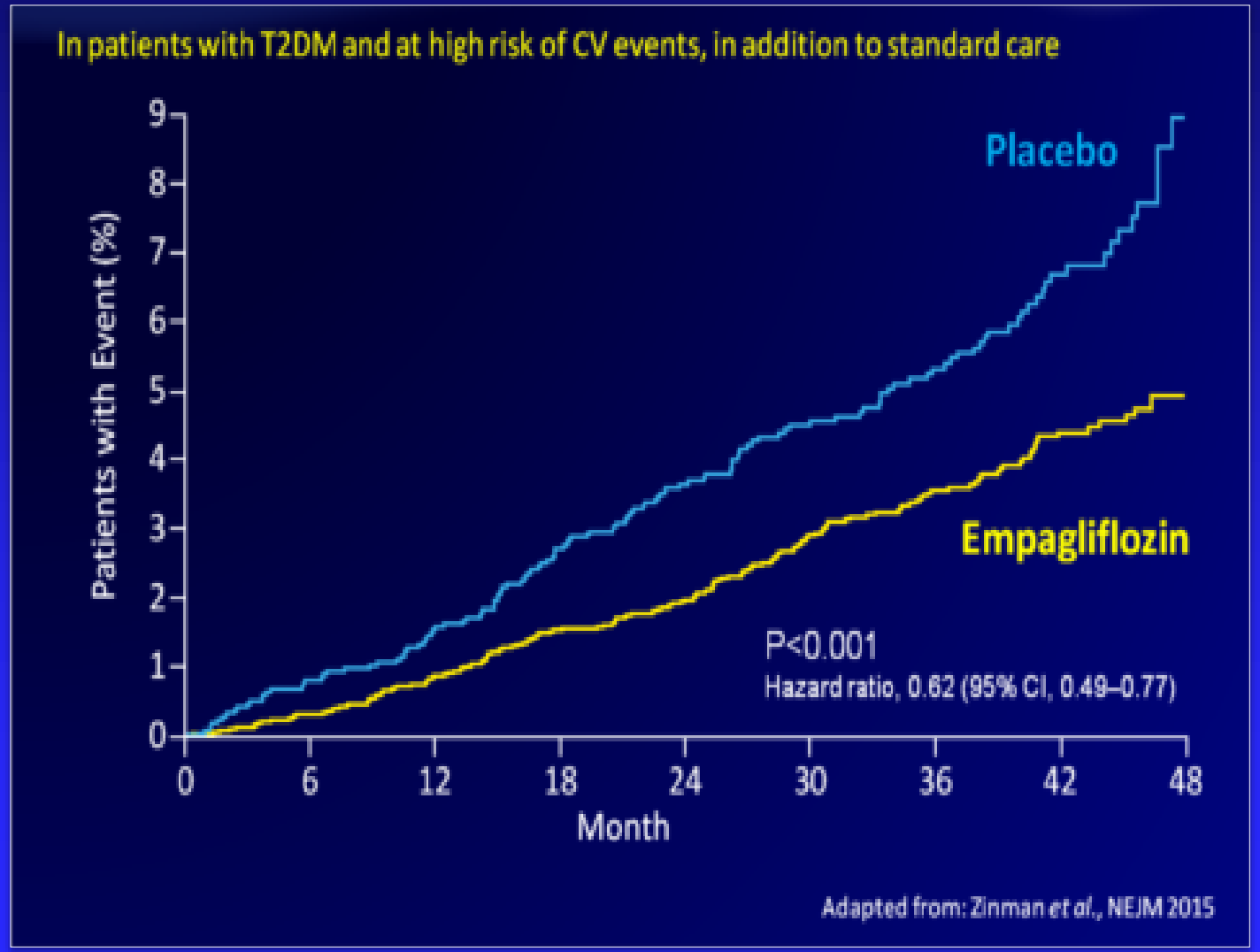
  Empagliflozin 10 mg • Empagliflozin 25 mg • Placebo
- Primary composite endpoint: CV mortality, nonfatal MI, nonfatal stroke
- Key secondary composite outcome: Primary plus hospitalization for UA
- Median 3.1-yr follow-up

Select baseline characteristics		
	Placebo (n=2,333)	Empagliflozin (n=4,687)
Age, yrs	63.2	63.1
CV history	2,307 (98.9%)	4,657 (99.4%)
A1C	8.08%	8.07%
Dual glucose-lowering therapy	1,148 (49.2%)	1,380 (29.4%)

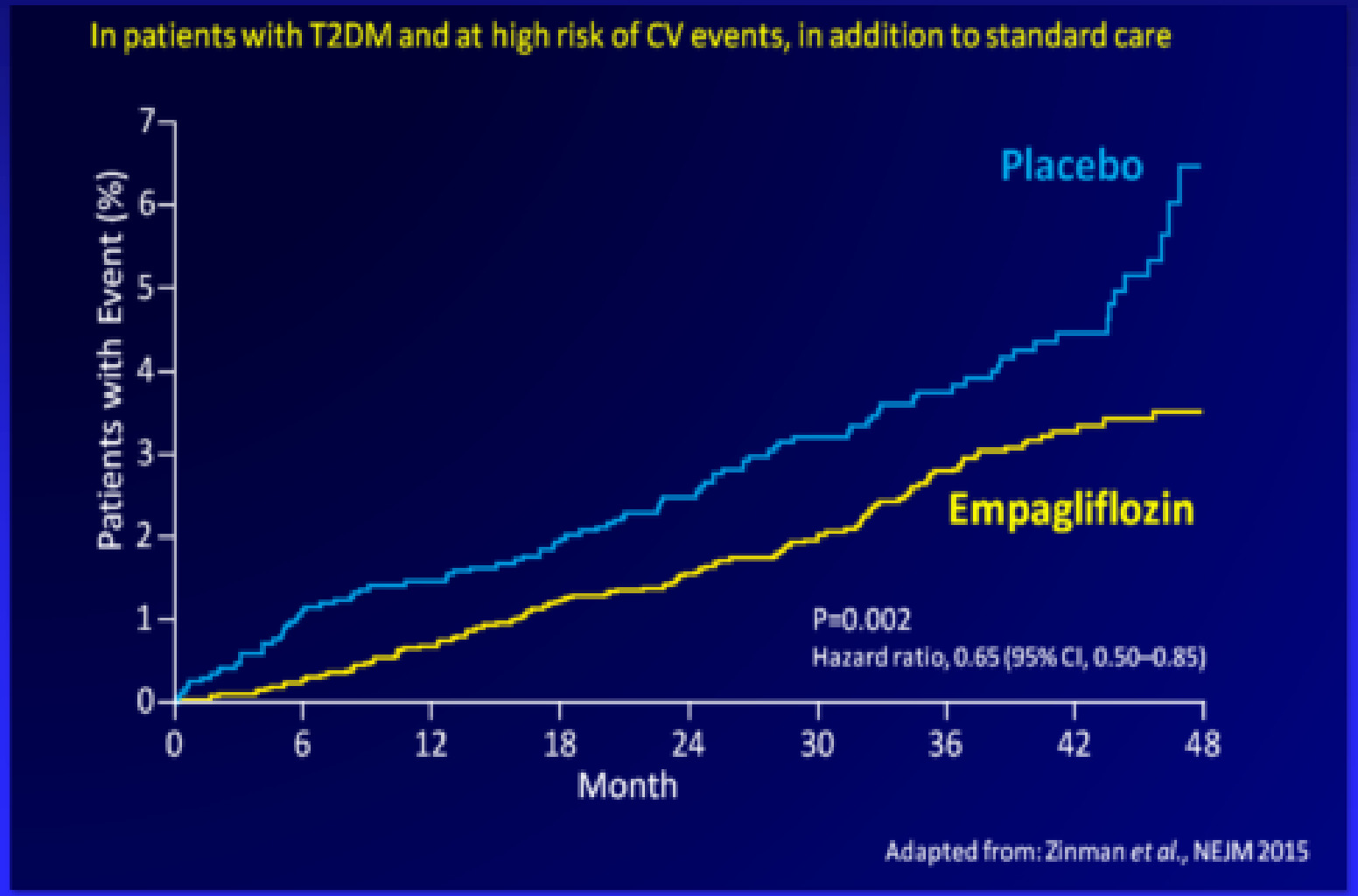
CVOT=cardiovascular outcome trial; UA=unstable angina

Zinman B, et al; for the EMPA-REG OUTCOME Investigators. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1504720.

EMPA-REG OUTCOME: Cumulative Incidence of Death from CV Causes



EMPA-REG OUTCOME: Hospitalization for Heart Failure



Take Home Messages:

Glucose Lowering and CV Risk

Targets matter - A1C:

- ***As low as possible***
- ***As early as possible***
- ***As long as possible***
- ***As safely as possible***
- ***As rationally as possible***

Strategies matter:

- ***Avoidance of hypoglycemia***
- ***BP and lipid control***
- ***Choice of anti hyperglycemic agents***

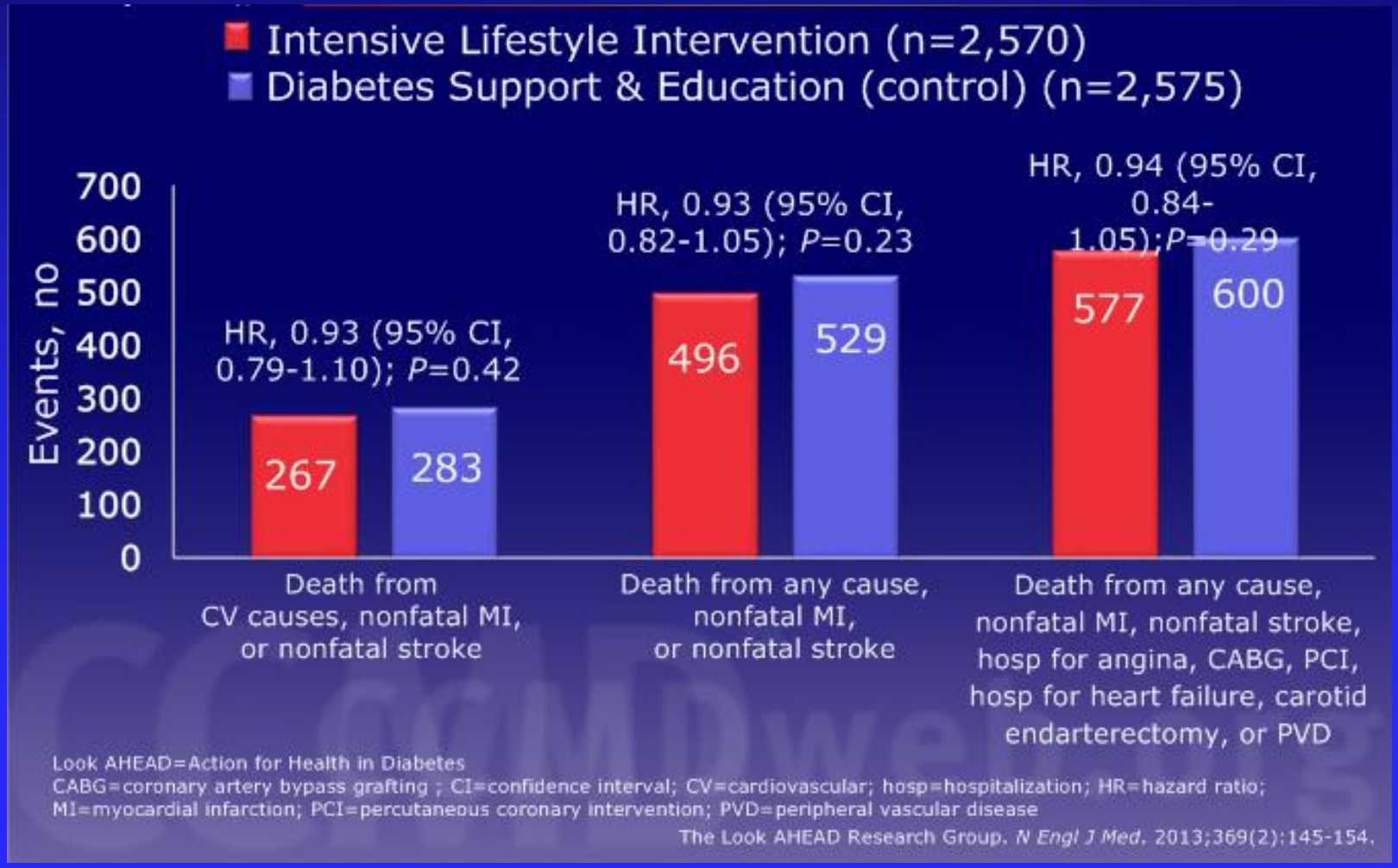
Intensive Glycemic Control and CV Risk in Diabetes.

... After observation and analysis, when you find that anything agrees with reason and is conducive to the good and benefit of one and all, then accept it and live up to it.

Lord Buddha (c. 563- c. 483 BC)

Thank You

Look AHEAD: No Reduction in Secondary CV Outcomes with Lifestyle Changes



Look AHEAD=Action for Health in Diabetes
CABG=coronary artery bypass grafting ; CI=confidence interval; CV=cardiovascular; hosp=hospitalization; HR=hazard ratio; MI=myocardial infarction; PCI=percutaneous coronary intervention; PVD=peripheral vascular disease

The Look AHEAD Research Group. *N Engl J Med*. 2013;369(2):145-154.

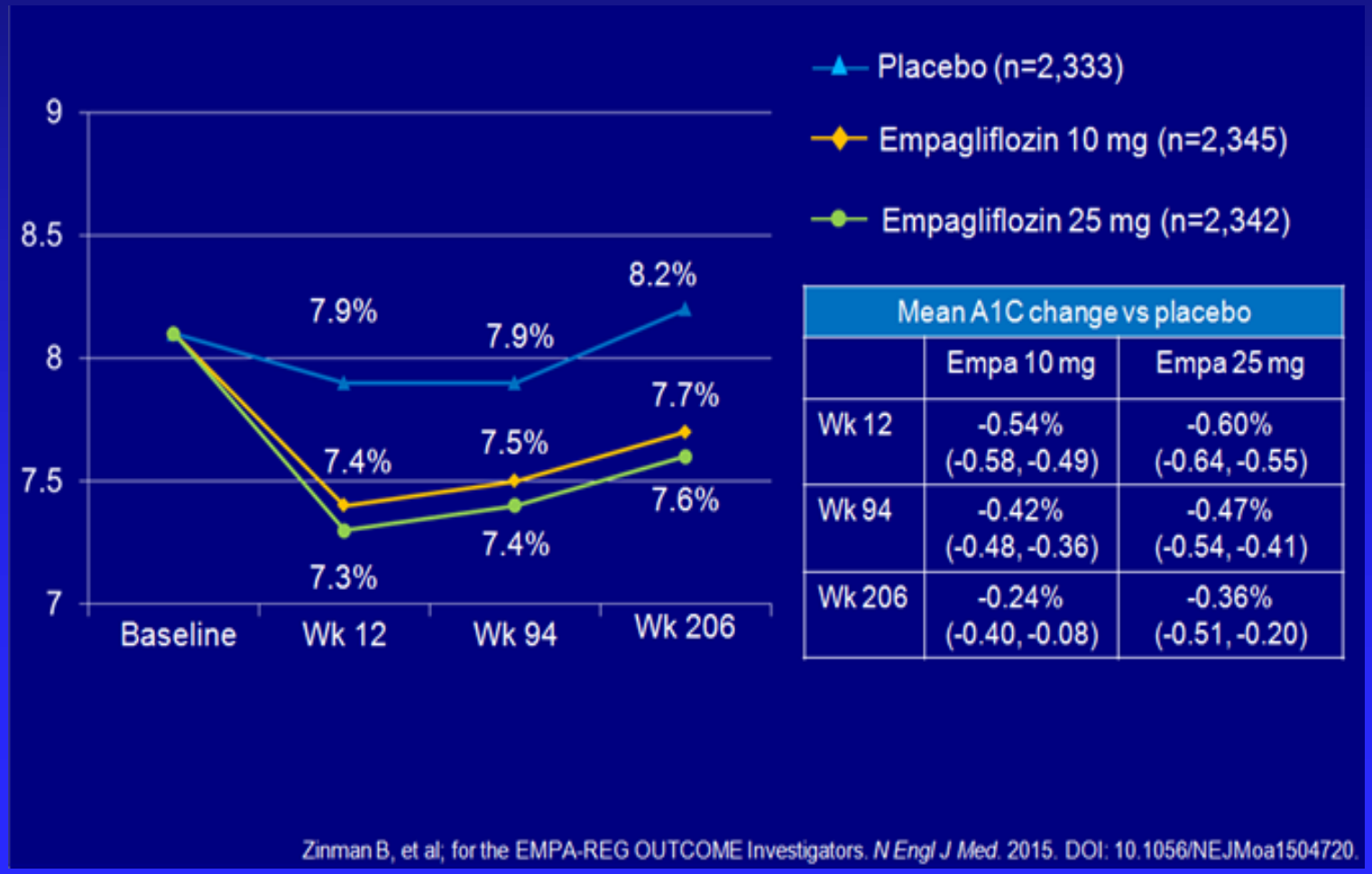
CV Safety of TZDs

- ***TZDs cause or exacerbate heart failure in some patients[1]***
- ***CV meta-analyses in 2007 suggested differing effects on CV outcomes***
- ***Pioglitazone was associated with significant 16% reduction in 3P-MACE (as a secondary endpoint) vs placebo in PROactive[2]***
- ***Rosiglitazone open-label RECORD data showed no increase in CV death[1]***
- ***FDA reduced the safety restrictions on rosiglitazone impos r CV sa***

The FDA has mandated that each agent within this class be evaluated individually.

1 AVANDIA US Prescribing information

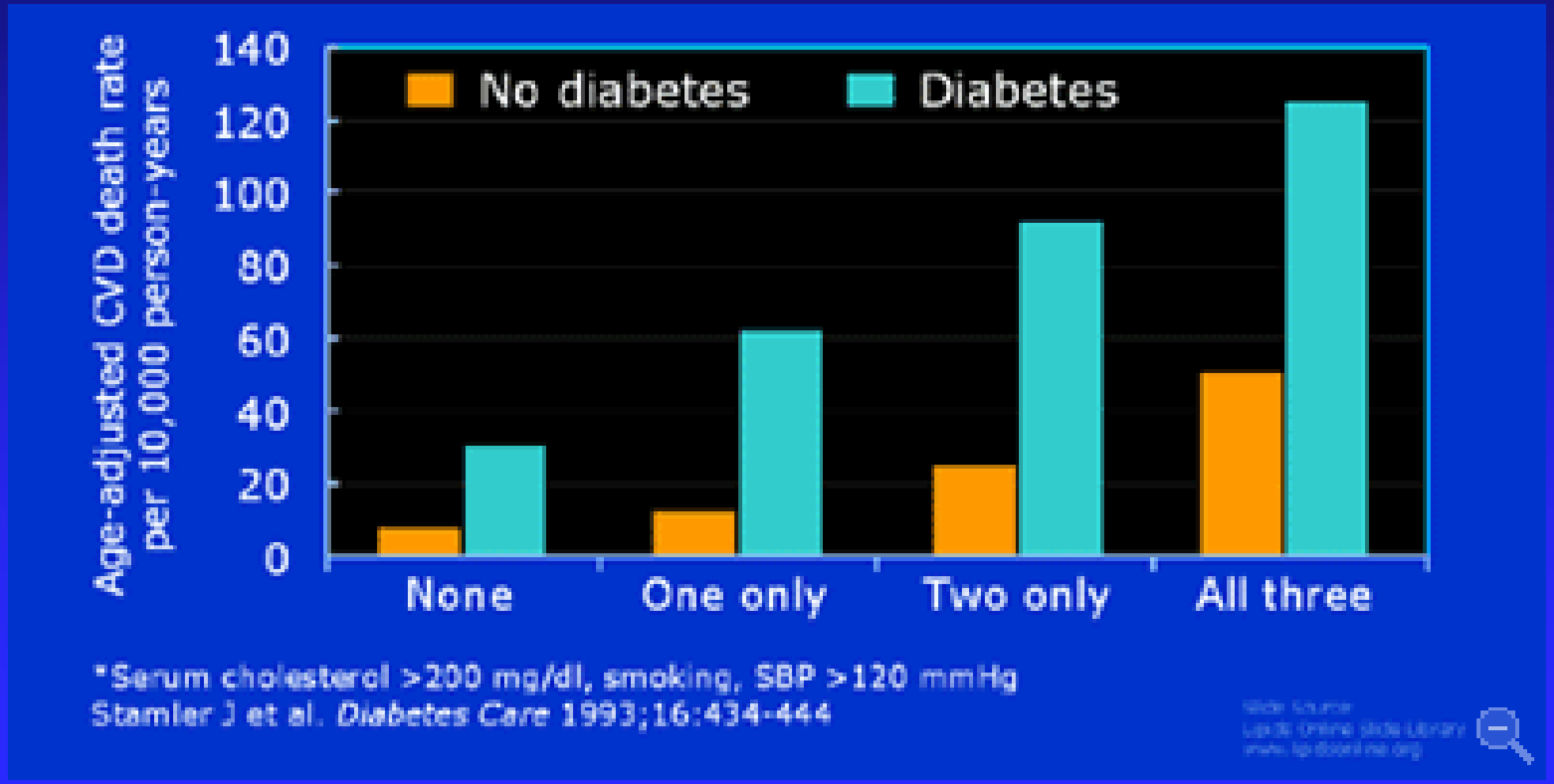
A1C Lowering with Empagliflozin vs Placebo in High-Risk Patients with Type 2 Diabetes



Mean A1C change vs placebo		
	Empa 10 mg	Empa 25 mg
Wk 12	-0.54% (-0.58, -0.49)	-0.60% (-0.64, -0.55)
Wk 94	-0.42% (-0.48, -0.36)	-0.47% (-0.54, -0.41)
Wk 206	-0.24% (-0.40, -0.08)	-0.36% (-0.51, -0.20)

Zinman B, et al; for the EMPA-REG OUTCOME Investigators. *N Engl J Med.* 2015. DOI: 10.1056/NEJMoa1504720.

Multiple Risk Factors and Mortality in Men:
MRFIT Study



Impact of Intensive Glycemic Therapy on T2DM Outcomes