Balancing CV Risk & Benefit with Diabetes Therapies: A New Outlook for Patient Care

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Guidance for Diabetes Drug Development 1990-2008

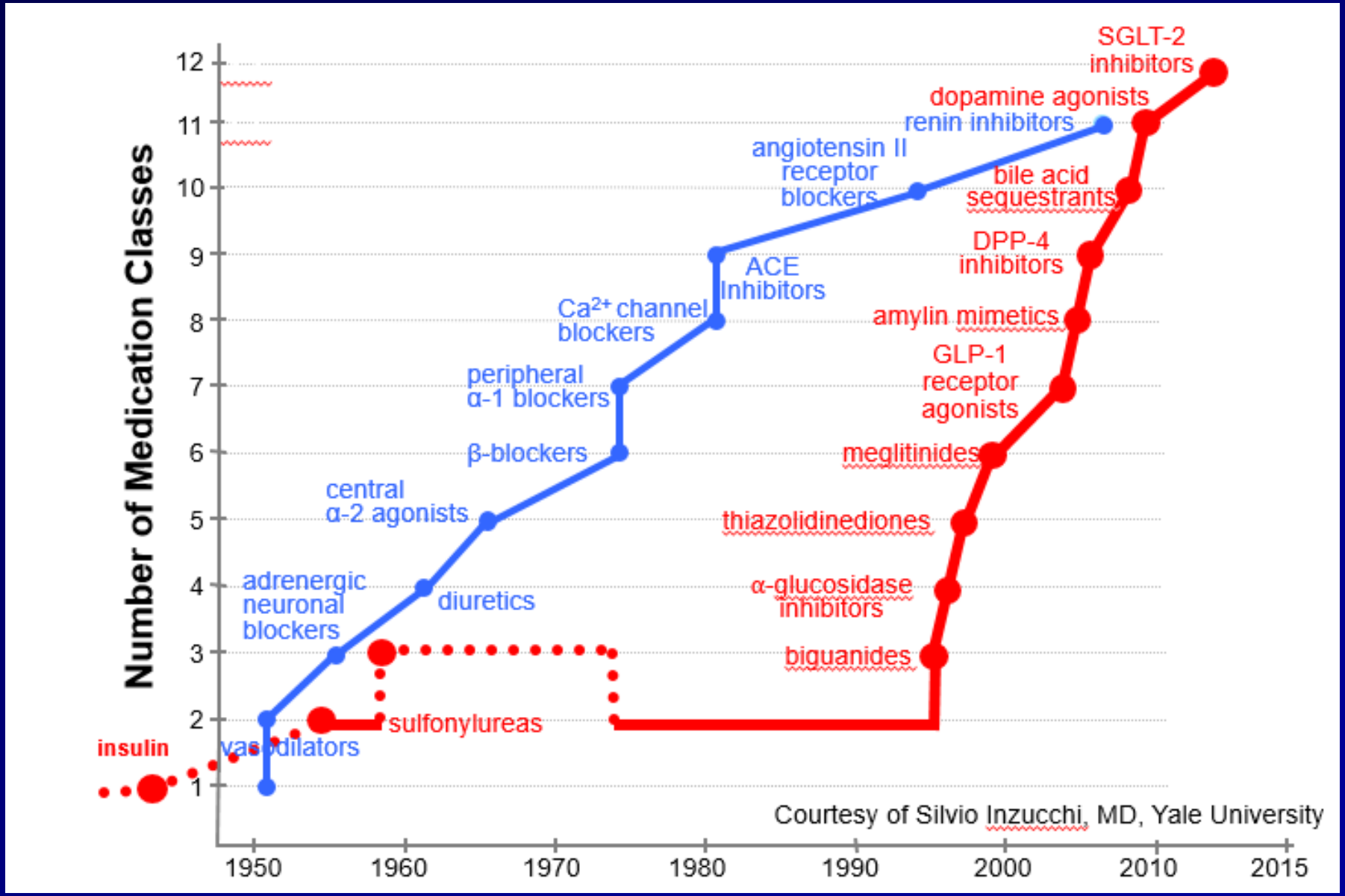
- ICH Guidelines:
  - 1500 patients exposed
  - 300-600 x 6 months
  - 100 x 1 year

- Approval based on as little as **250 patient-years** of exposure

Paradigm Shift Underpinning Regulatory Change

- Increasing incidence/prevalence of T2DM
  - >10% of US adult population
- Growing awareness of CV impact of T2DM
- Proliferation of medications available
- Numerous examples of adverse drug effects
  - On target
  - Off target

Half-Century of HTN & T2DM Medications in US



Present FDA Regulatory Guidance for Drugs for Type 2 Diabetes

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
December 17, 2008

Media Inquiries:
Karen Riley, 301-796-4674
Consumer Inquiries:
888-INFO-FDA

FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

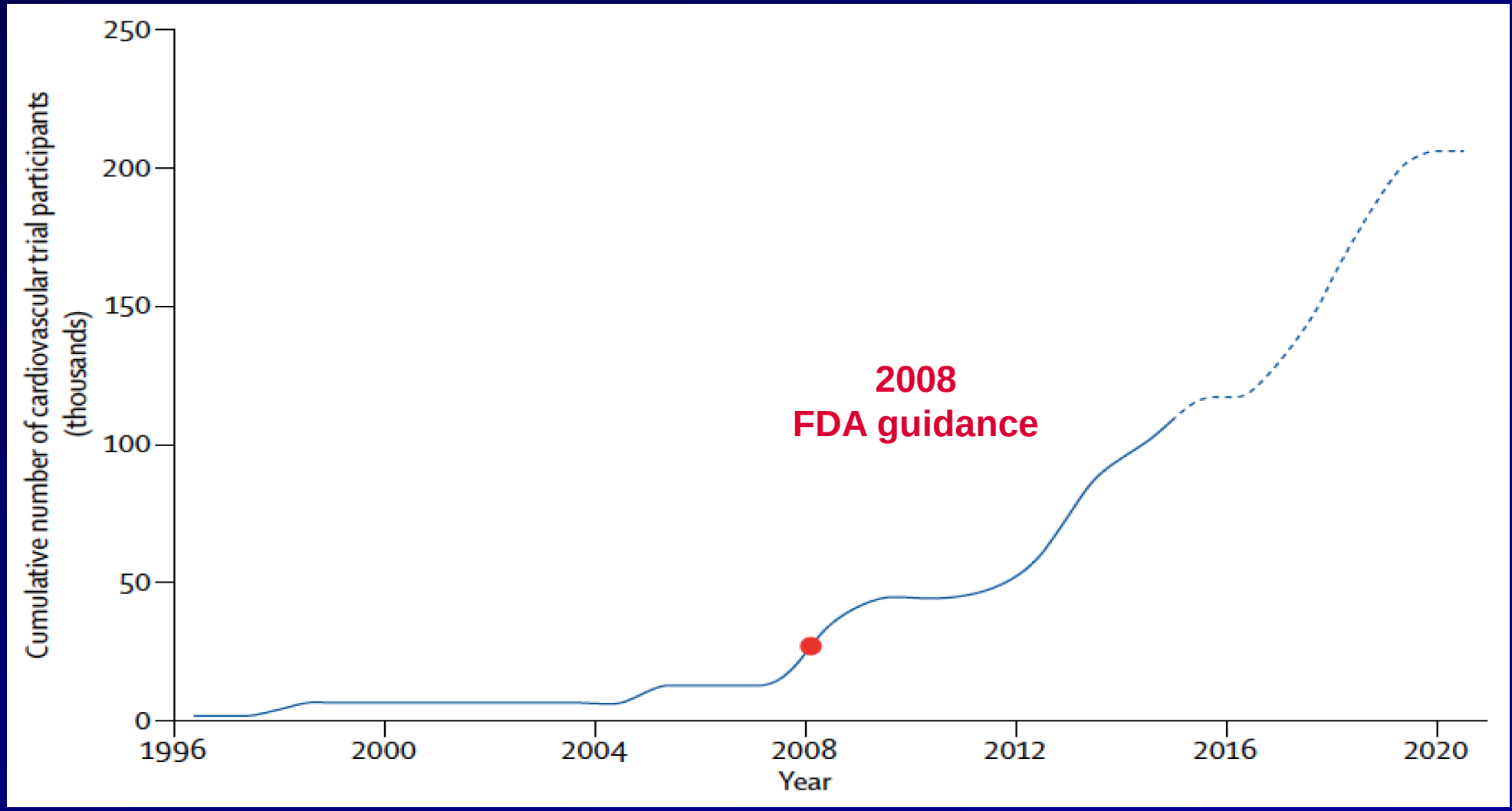
"…sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."

Requires ~15,000 pt-yrs of exposure

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116994.htm

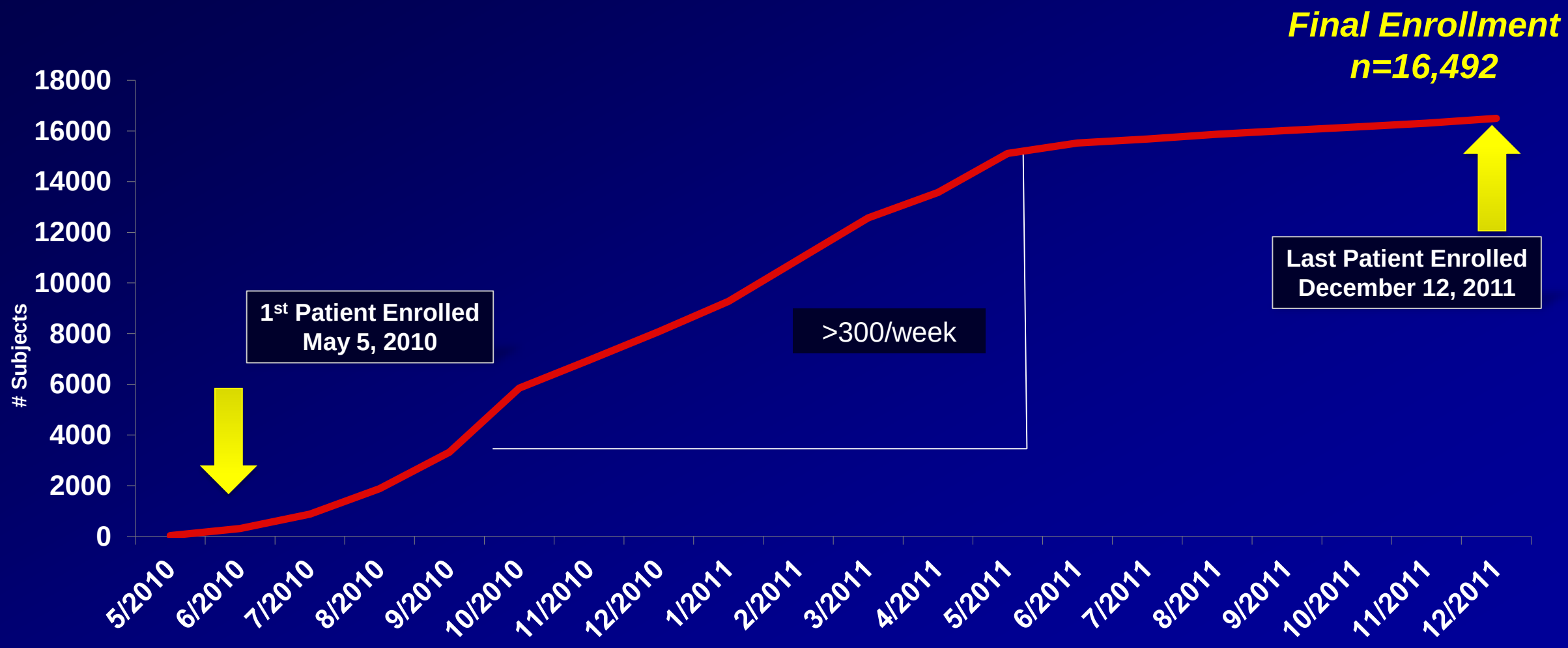
The sky is falling…

…it was just an acorn that fell.



Holman RR et al. Lancet 2014; 383: 2008–17.

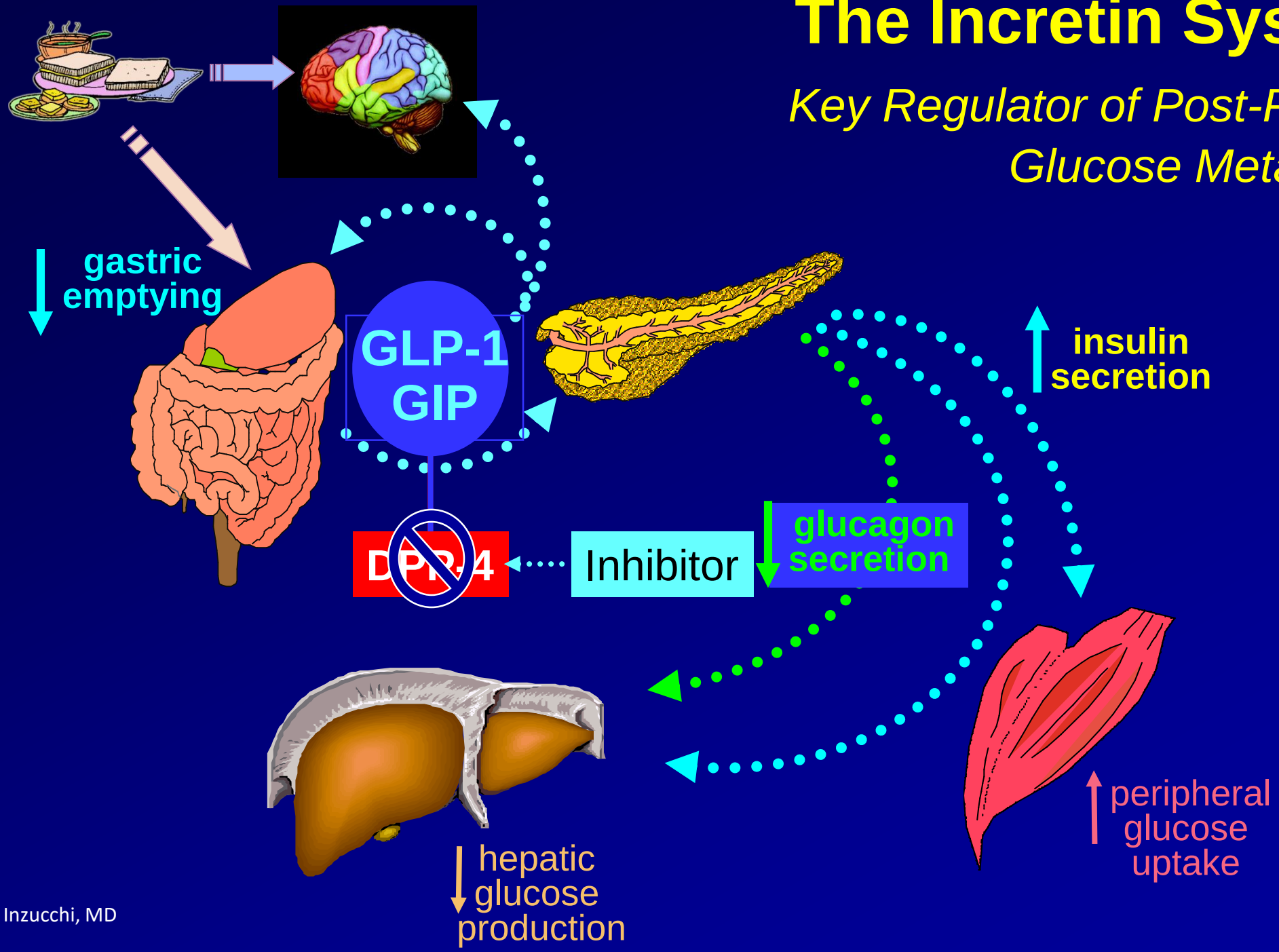
SAVOR-TIMI 53 Enrollment



Courtesy of Ben Scirica, MD, TIMI Study Group

The Incretin System:

Key Regulator of Post-Prandial Glucose Metabolism

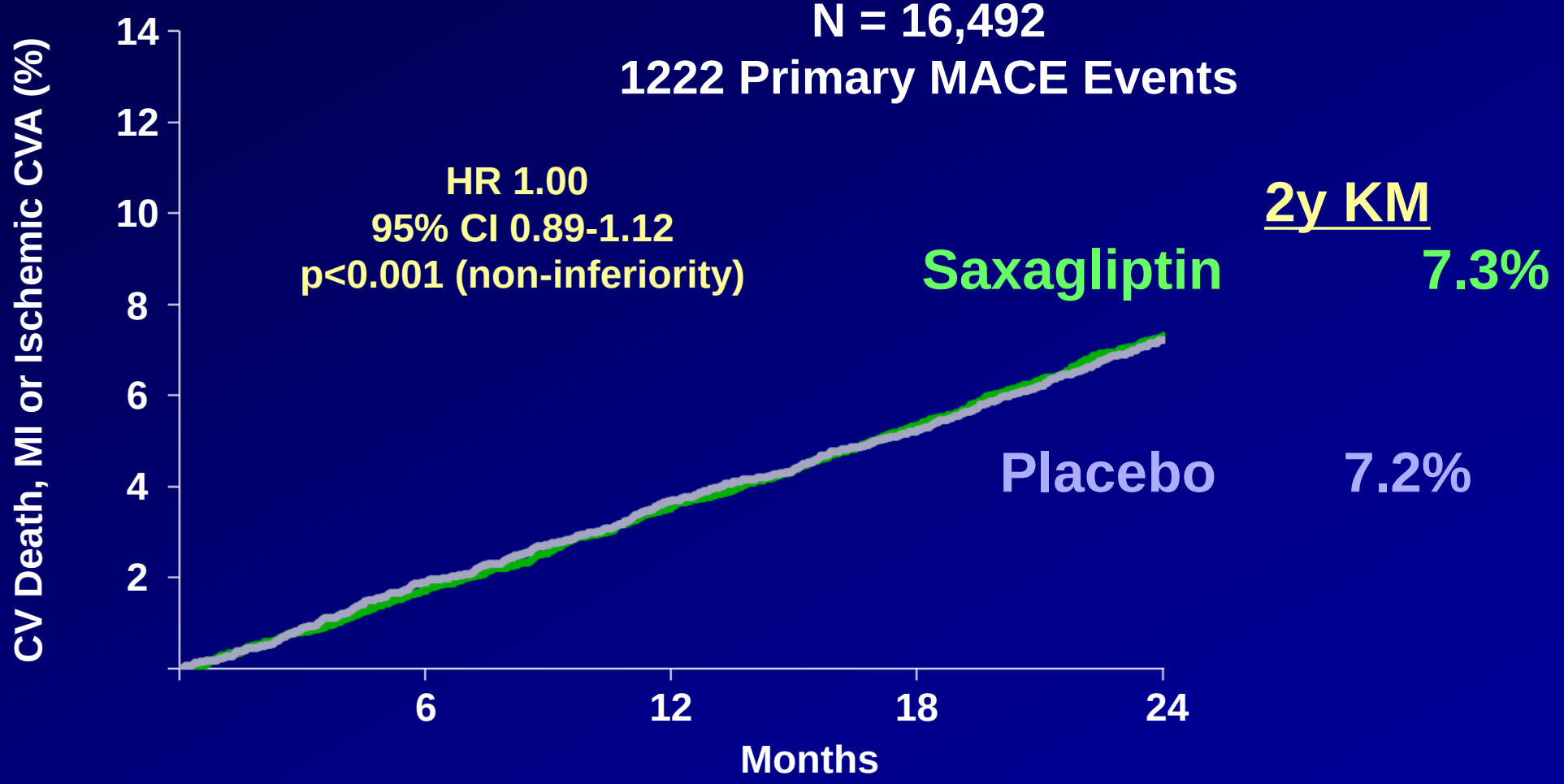


Courtesy, Silvio Inzucchi, MD

Incretin Modulators on US Market

DPP4-inhibitors	Sitagliptin
	Saxagliptin
	Alogliptin
	Linagliptin
GLP1-receptor agonists	Exenatide
	Liraglutide
	Albiglutide
	Exenatide ER
	Dulaglutide

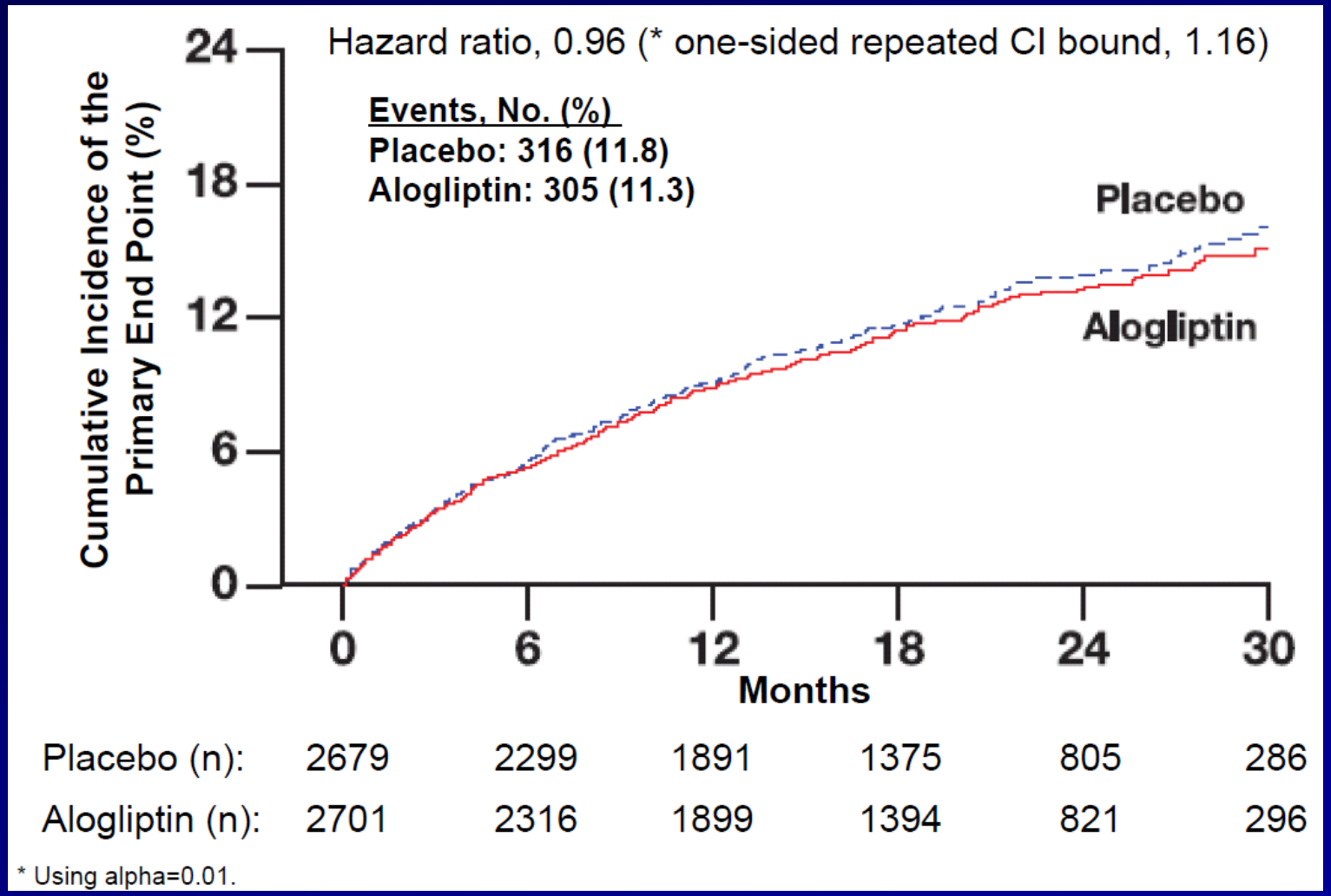
SAVOR TIMI 53-Primary Endpoint



Scirica BM, et al. N Engl J Med 2013; 369: 1317-1326.

Primary Endpoint

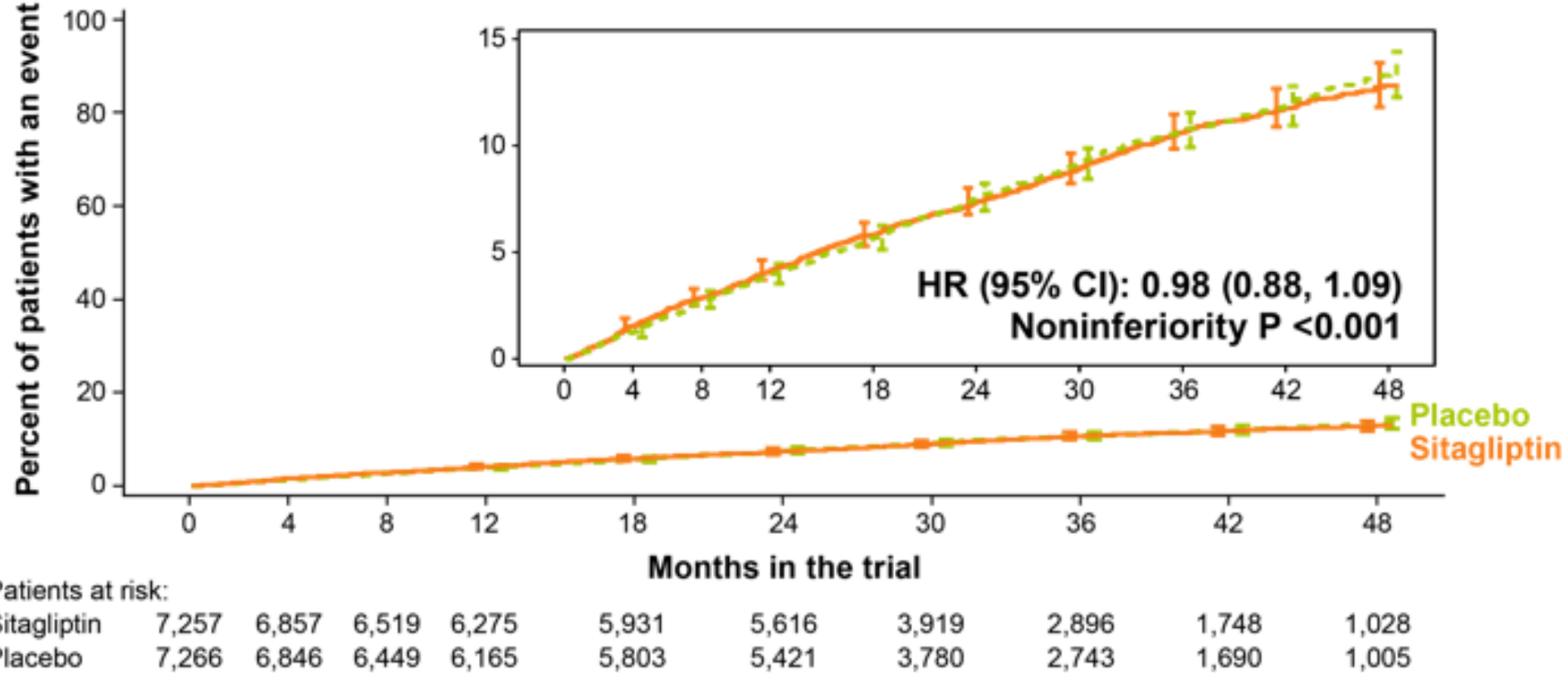
N = 5380



White WB, et. al. N Engl J Med. 2013; 369:1327

Primary Composite Cardiovascular Outcome*

Per Protocol Analysis for Noninferiority



Patients at risk:

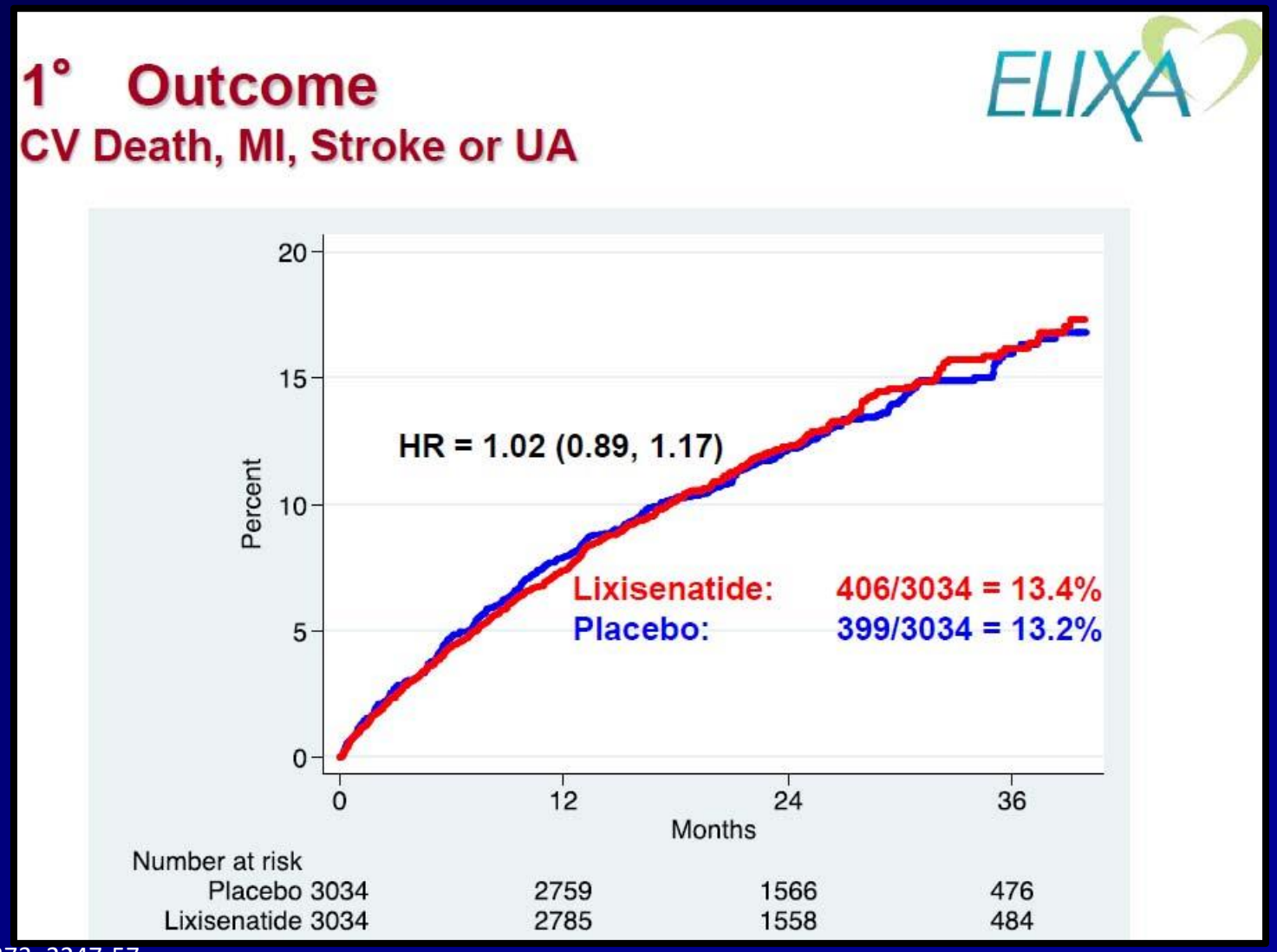
Sitagliptin	7,257	6,857	6,519	6,275	5,931	5,616	3,919	2,896	1,748	1,028
Placebo	7,266	6,846	6,449	6,165	5,803	5,421	3,780	2,743	1,690	1,005

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

Green JB et al. NEJM 2015;373: 232-42

TECOS TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

ELIXA: Lixisenatide* vs. Placebo Effects on CV Outcomes



Pfeffer MA et al. NEJM 2015; 373: 2247-57.

*Not FDA approved

Rare But Serious Adverse Drug Reactions Require Large Exposure…

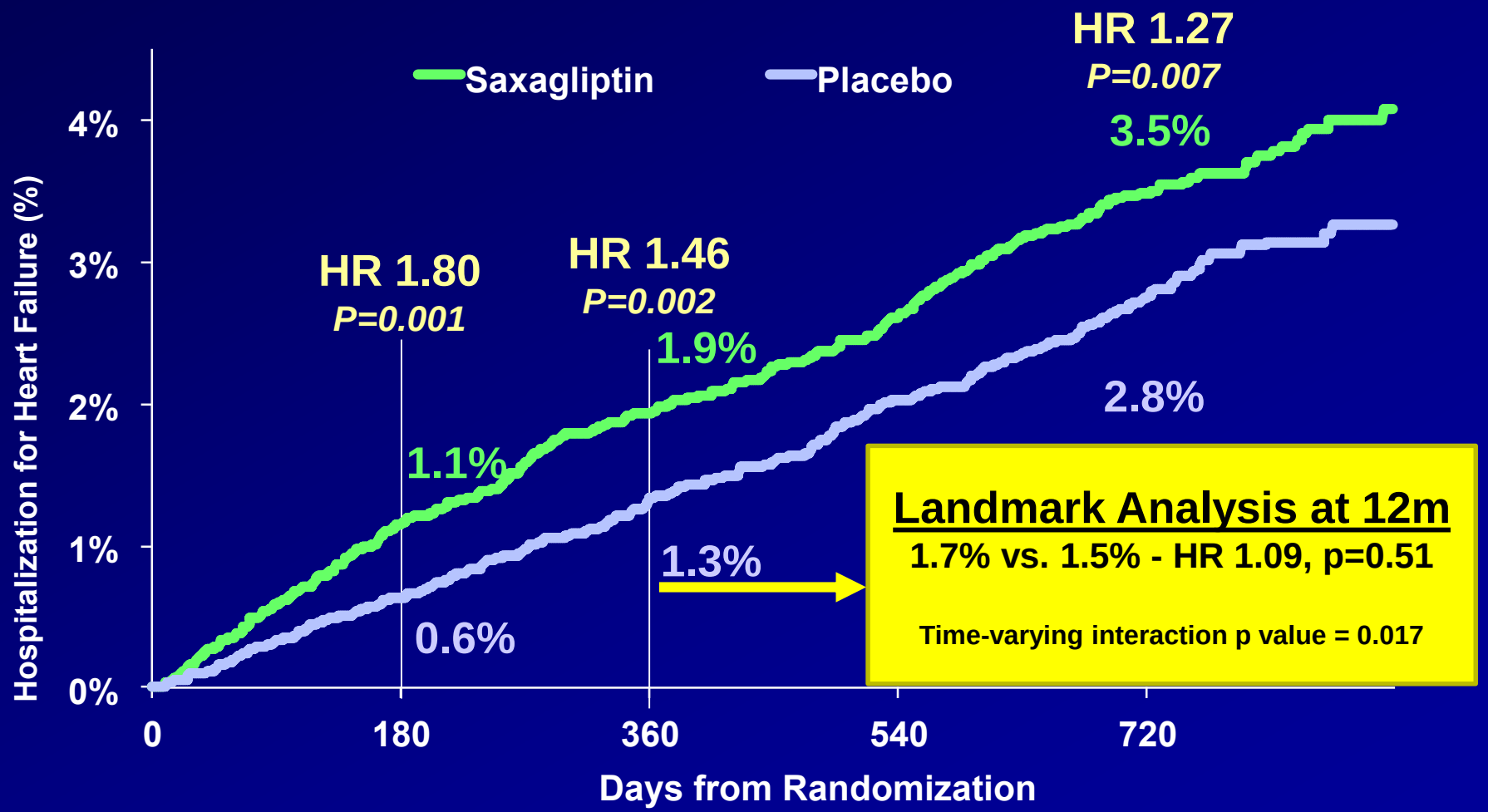
- Taspoglutide* (~600 pt years)
  - Nausea
  - Vomiting
  - Antibody formation
  - Anaphylactoid reactions
- Aleglitazar* (>14,000 patient years)
  - HF
  - Decline in eGFR
  - Bone fracture
  - GI Bleeds
- Fasiglifam* (~2000 patient years)
  - Drug-associated liver injury (10-fold increase in elevated LFTs)

Rosenstock J et al. Diabetes Care 2013; 36: 498–504.
Lincoff AM et al. JAMA 2014; 311: 1515-1525.

***Not FDA approved; development halted.**

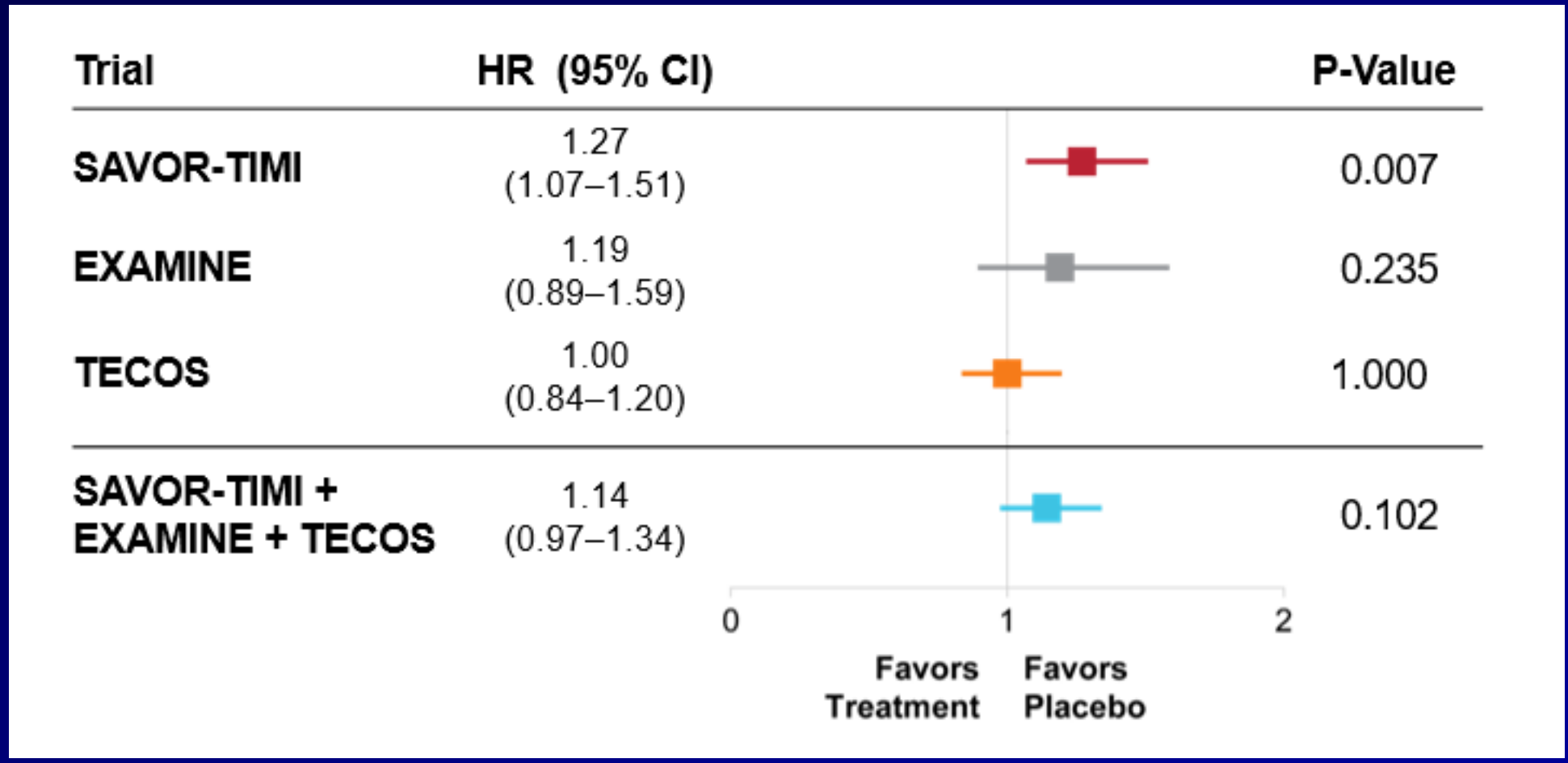
SAVOR TIMI 53-Hospitalization for Heart Failure

Time to the 1st occurrence of any hospitalization for heart failure; 517 events



Scirica BM, et al. Circulation 2014; 130:1579-88.

SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure

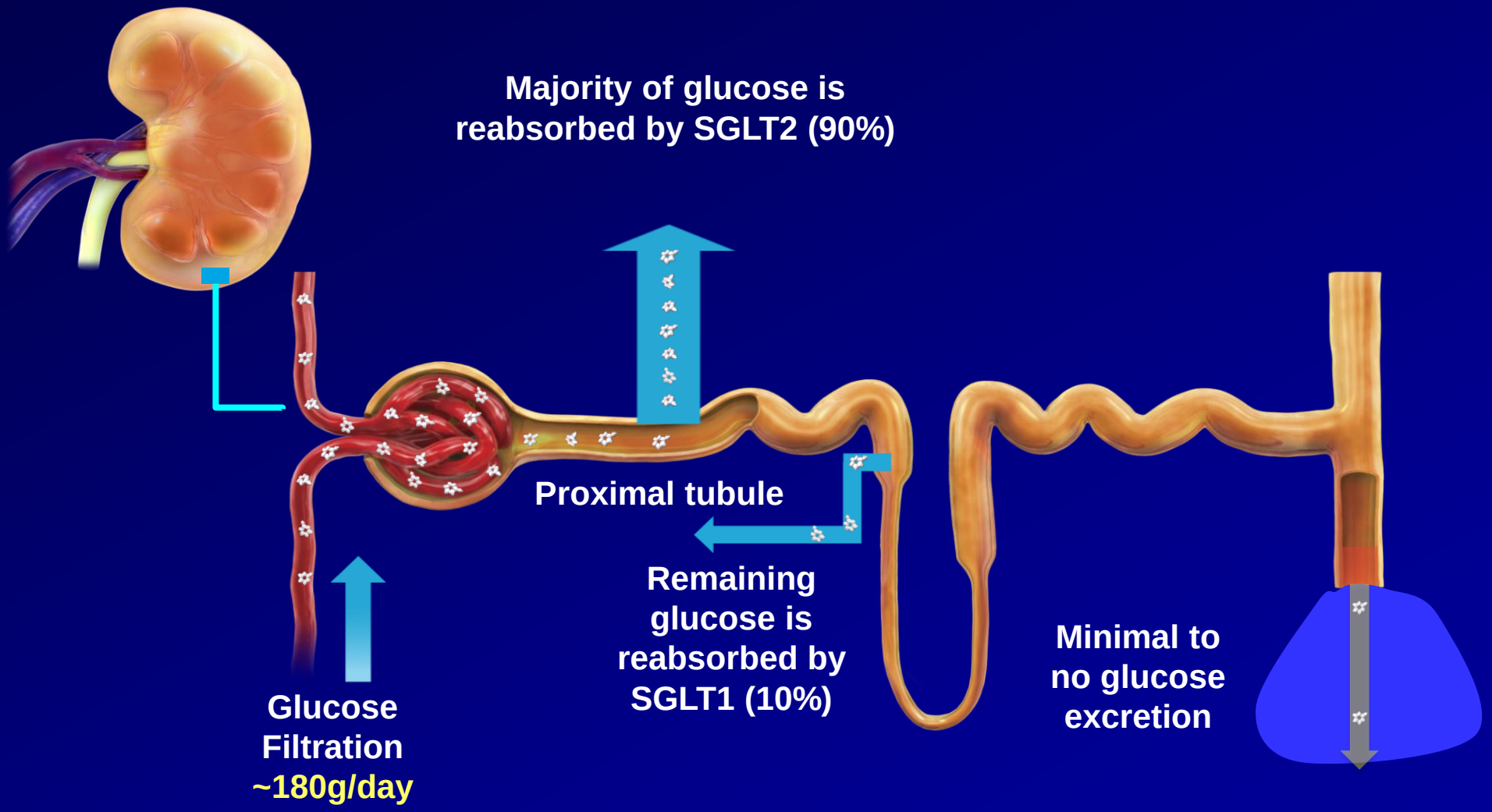


Test for heterogeneity for 3 trials: p=0.16, I^2=44.9

McGuire DK, et al. ESC 2015

TECOS TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Normal Renal Glucose Handling

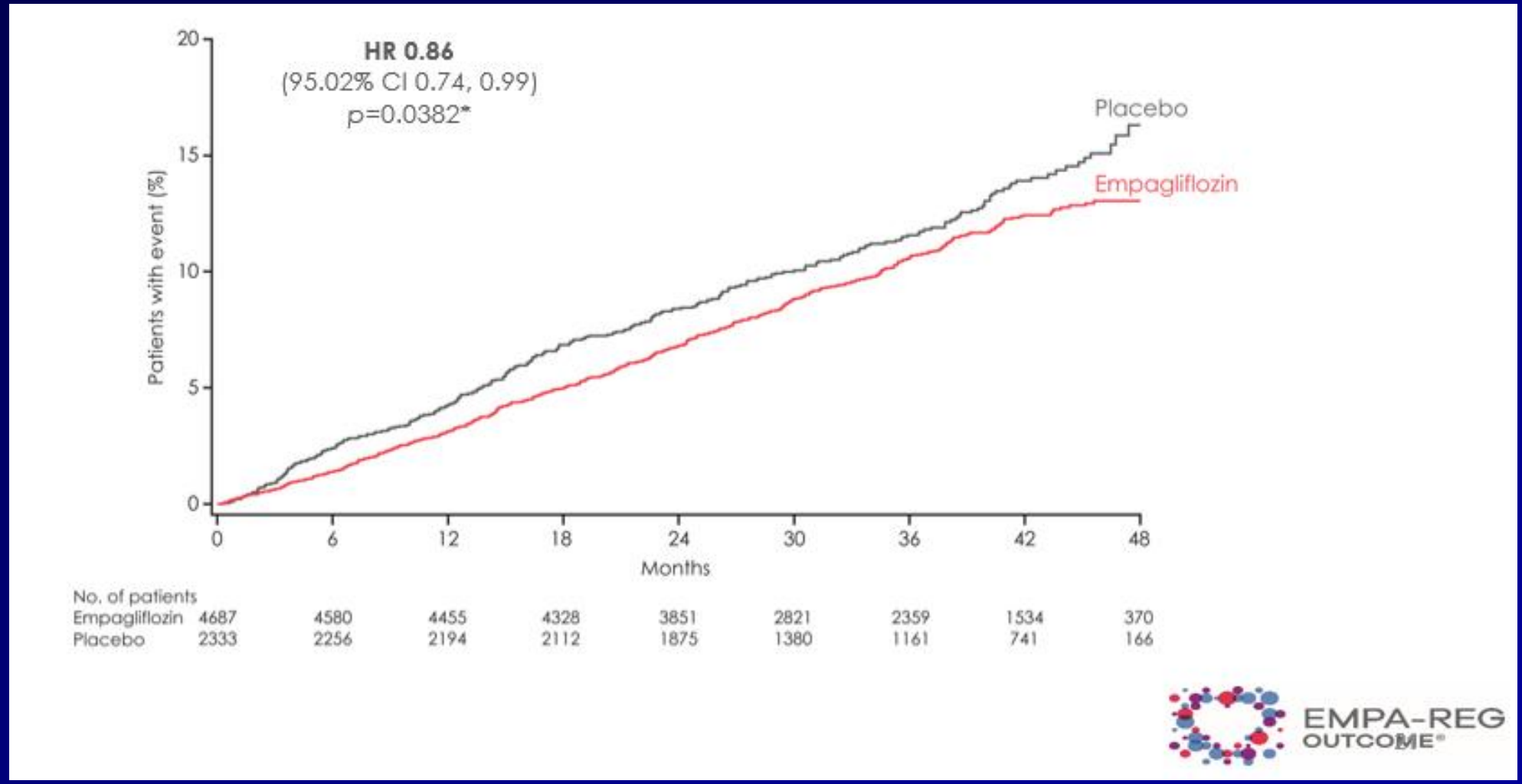


Wright EM. Am J Physiol Renal Physiol 2001; 280:F10–18;
Lee YJ, et al. Kidney Int Suppl 2007;106:S27–35;
Hummel CS, et al. Am J Physiol Cell Physiol 2011;300:C14–21.

SGLT2 Antagonists on US Market

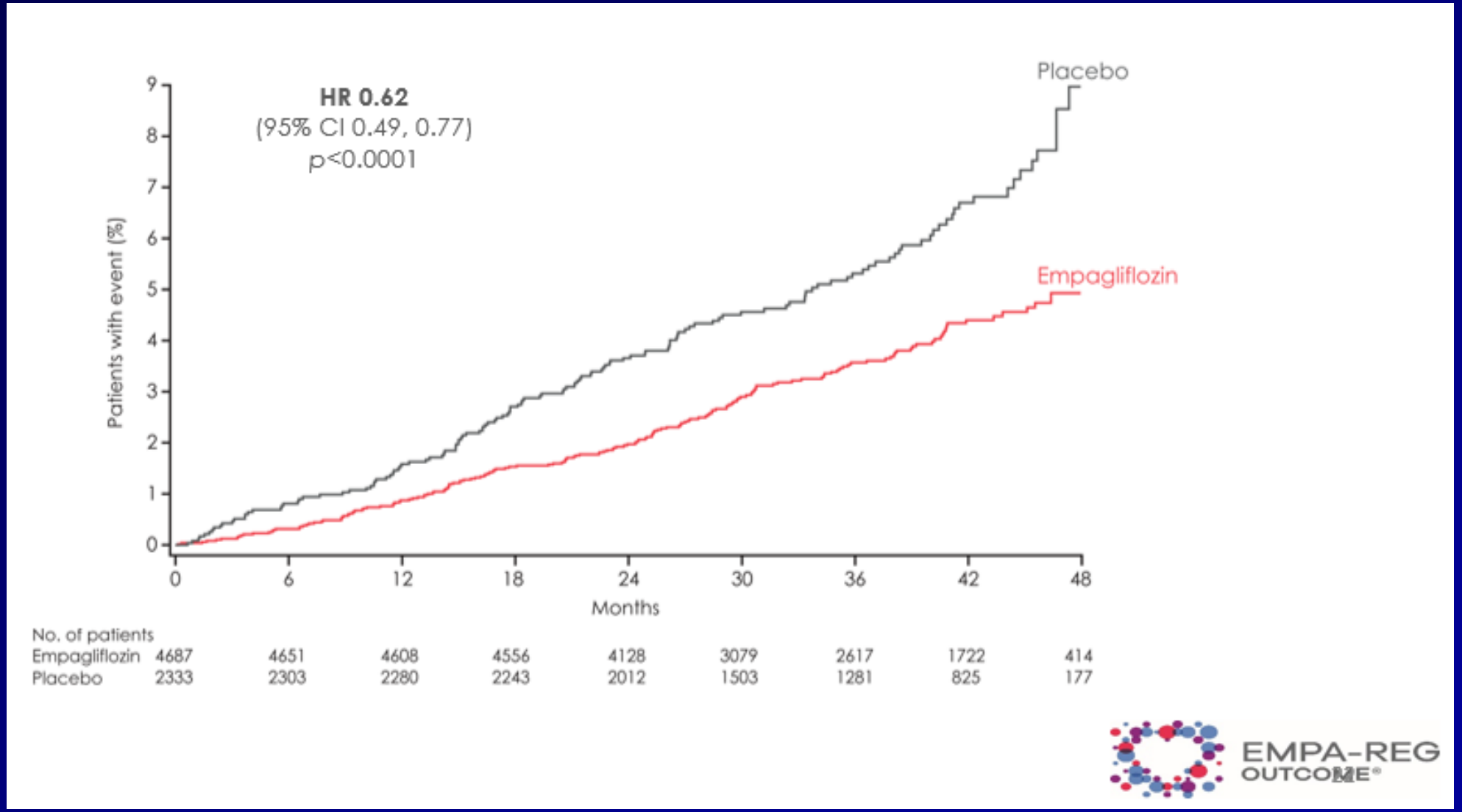
Canagliflozin
Dapagliflozin
Empagliflozin

Primary Outcome:
3-point MACE



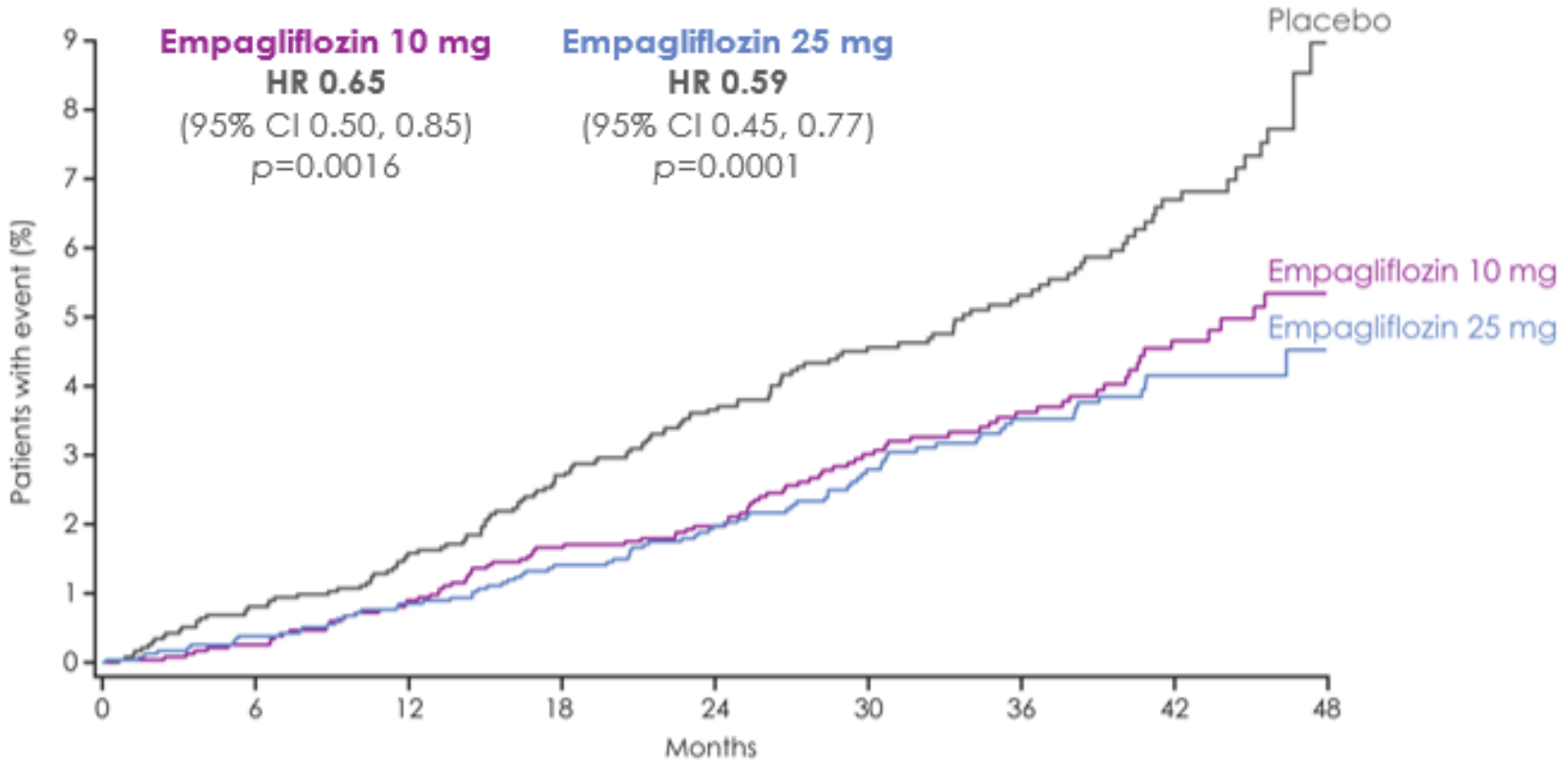
Zinman B et al. N Engl J Med 2015; 373: 2117-28

CV Death



Zinman B et al. N Engl J Med 2015; 373: 2117-28

CV Death

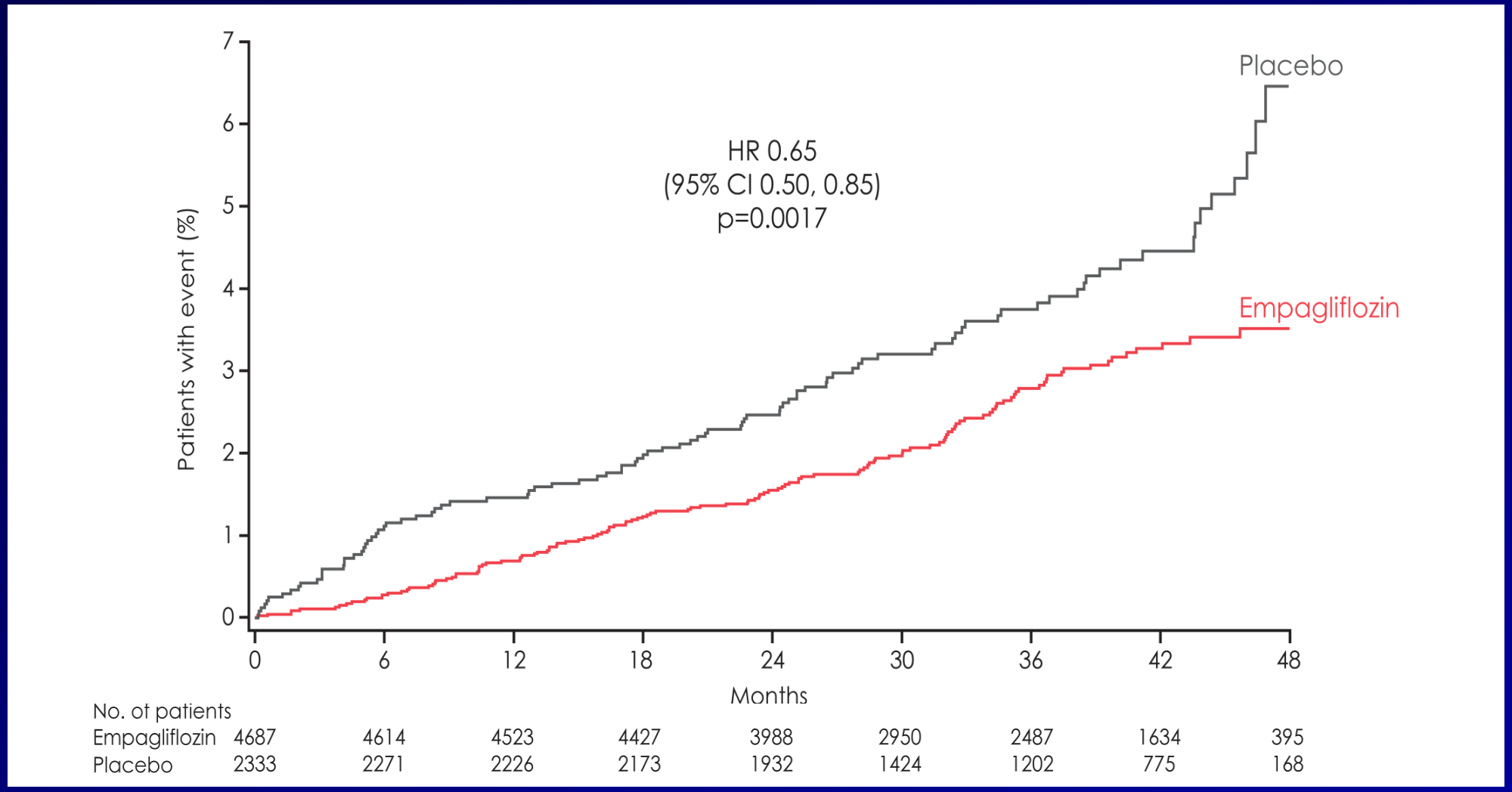


No. of patients									
Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

EMPA-REG OUTCOME®

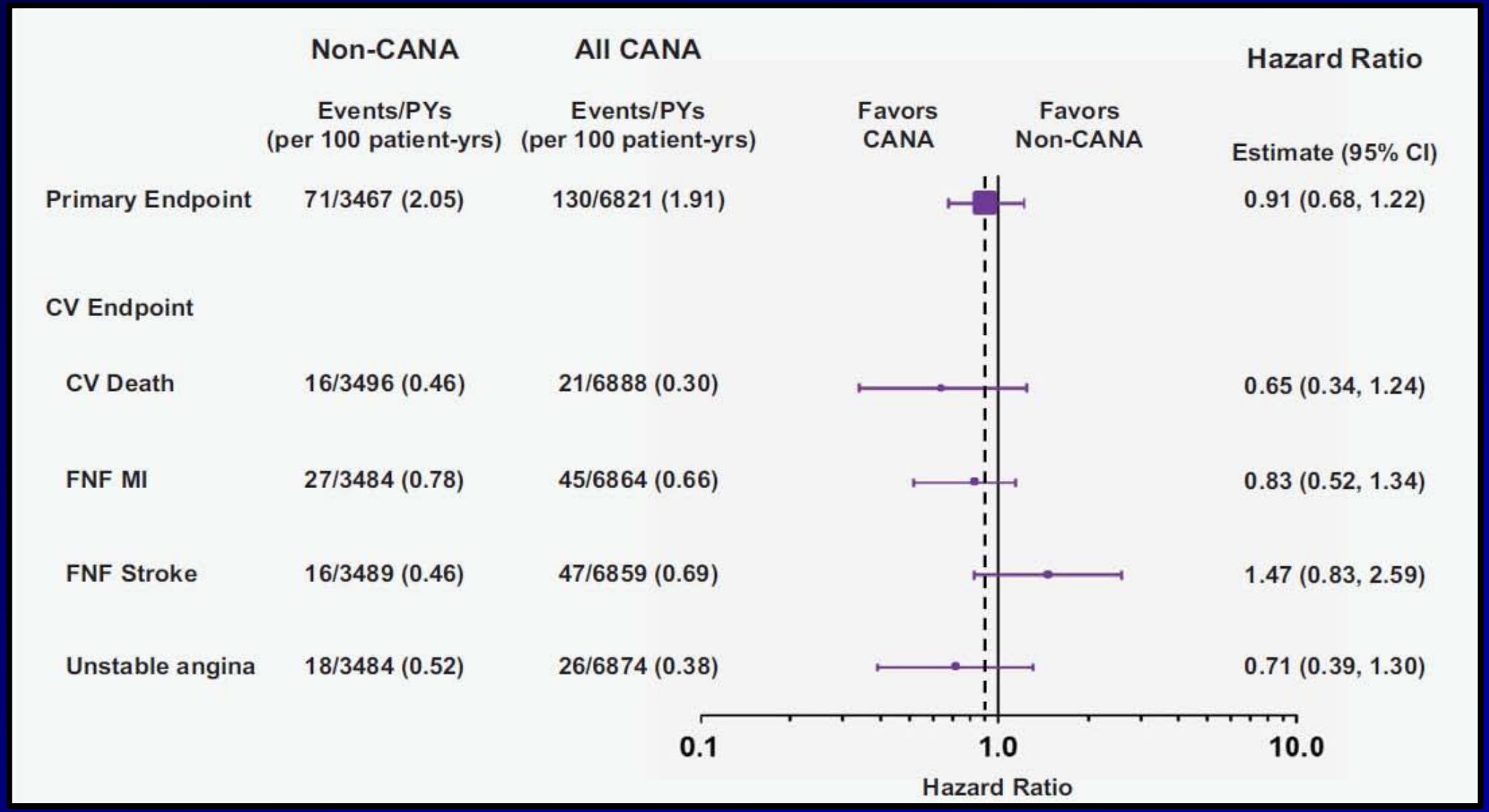
Zinman B et al. N Engl J Med 2015; 373: 2117-28

Hospitalization for Heart Failure



Zinman B et al. N Engl J Med 2015. 10.1056/NEJMoa1504720

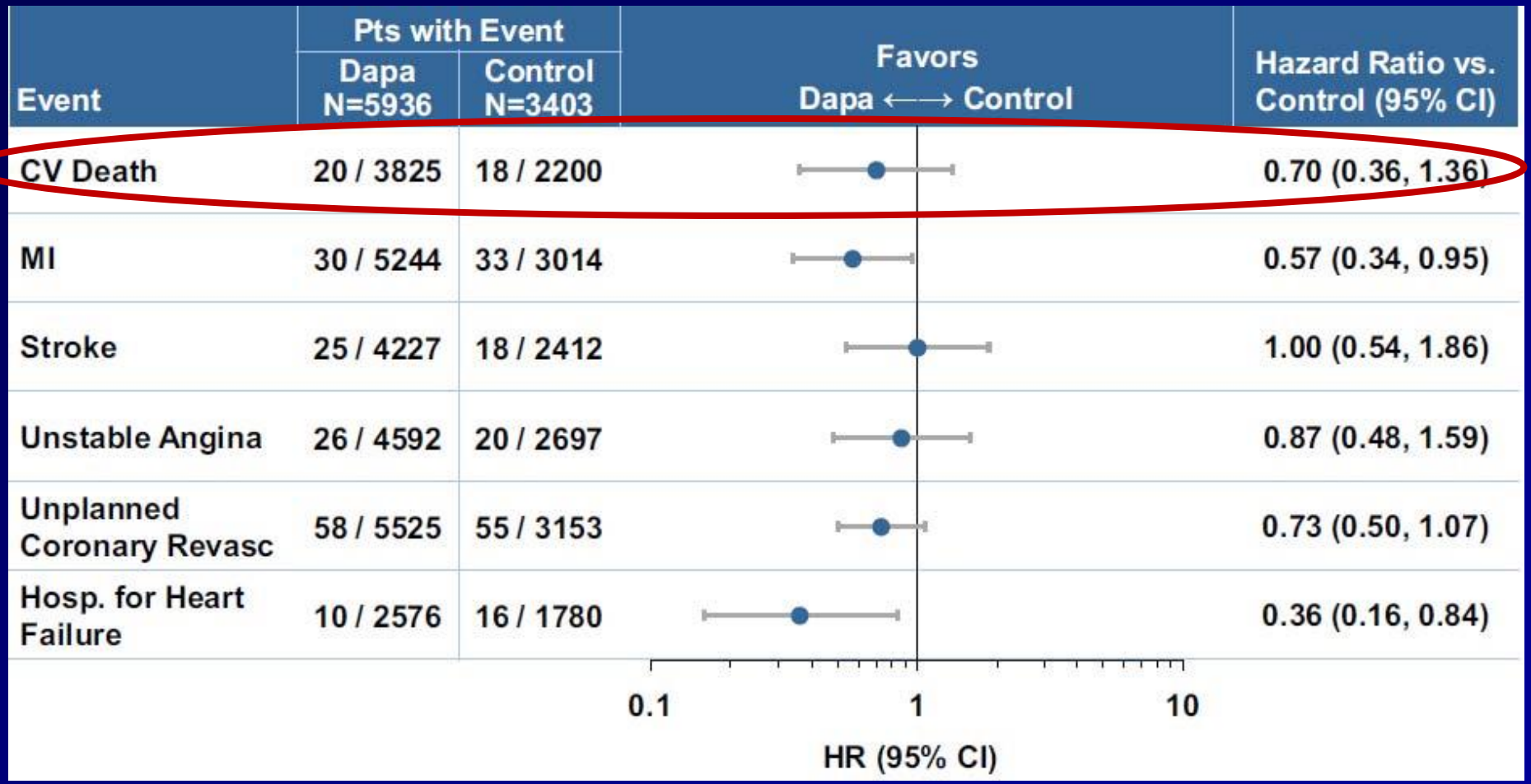
Composite Analyses of MACE Events: Canagliflozin



Canagliflozin Advisory Committee Meeting presentation. January 10, 2013. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf

Component Analyses of MACE Events: Dapagliflozin

Event	Pts with Event: Dapa N=5936	Pts with Event: Control N=3403	Hazard Ratio vs. Control (95% CI)
CV Death	20 / 3825	18 / 2200	0.70 (0.36, 1.36)
MI	30 / 5244	33 / 3014	0.57 (0.34, 0.95)
Stroke	25 / 4227	18 / 2412	1.00 (0.54, 1.86)
Unstable Angina	26 / 4592	20 / 2697	0.87 (0.48, 1.59)
Unplanned Coronary Revasc	58 / 5525	55 / 3153	0.73 (0.50, 1.07)
Hosp. for Heart Failure	10 / 2576	16 / 1780	0.36 (0.16, 0.84)



http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm262994.pdf

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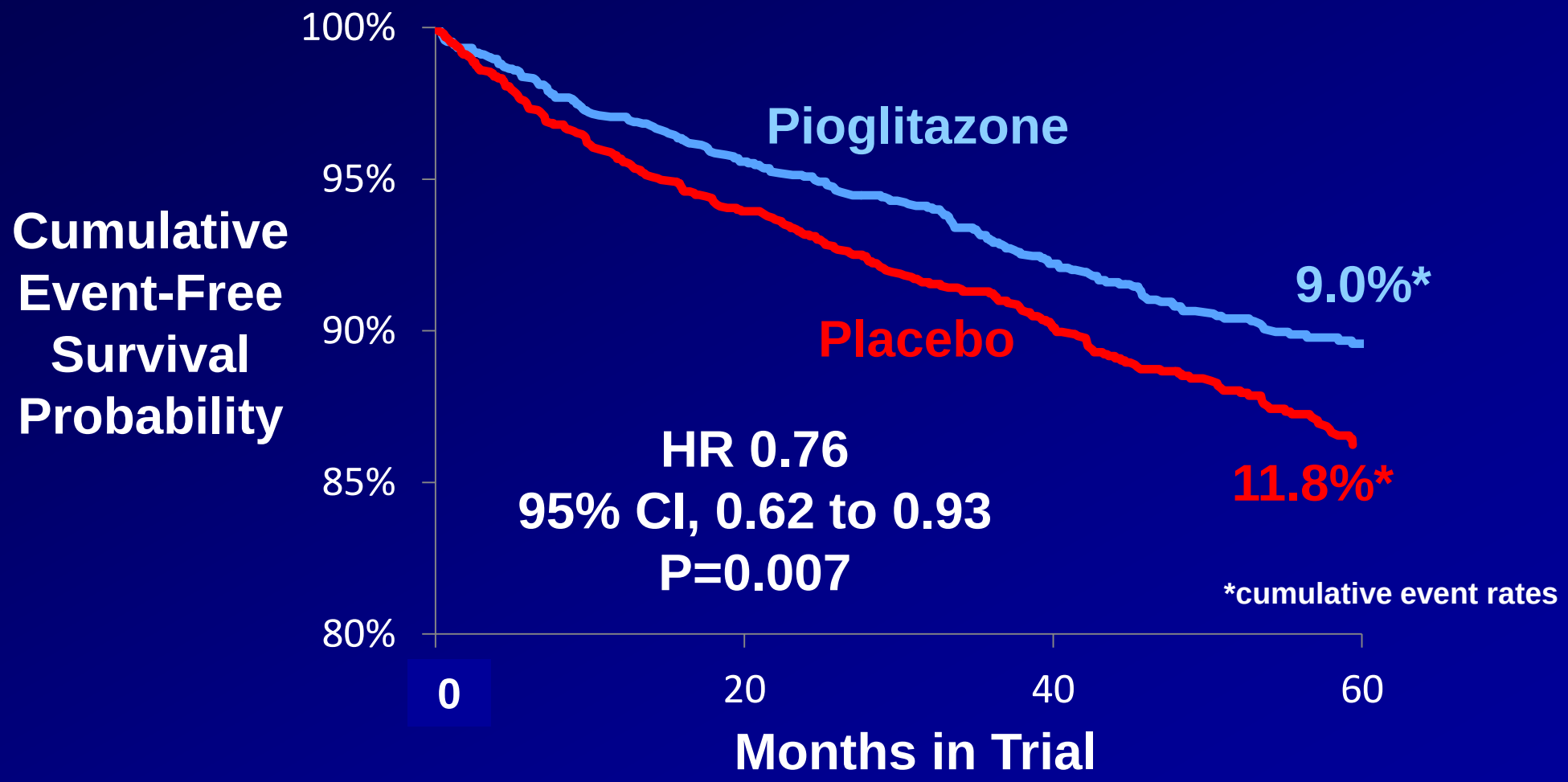
IRIS Primary Outcome



Kernan WN *et al. N Engl J Med*, published on-line Feb 17, 2016 DOI: 10.1056/NEJMoa1506930

Hot off the Press…

company announcement

Victoza® significantly reduces the risk of major adverse cardiovascular events in the LEADER trial

Bagsværd, Denmark, 4 March 2016 - Novo Nordisk today announced the top-line results from the LEADER trial, which investigated the cardiovascular safety of Victoza® (liraglutide) over a period of up to 5 years in more than 9,000 adults with type 2 diabetes at high risk of major adverse cardiovascular events. The trial compared the addition of either Victoza® or placebo to standard of care and met the primary endpoint of showing non-inferiority as well as demonstrating superiority, with a statistically significant reduction in cardiovascular risk. The primary endpoint of the study was defined as the composite outcome of the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The superior reduction of major adverse cardiovascular events demonstrated by Victoza® was derived from all three components of the endpoint.

Conclusions

- Diabetes has significant associated CV morbidity and mortality
- Role of glucose control in CVD risk mitigation remains uncertain
  - What drugs/strategies; what intensity; what timing
  - Side effects-both on- and off-target
  - Imperative to at a minimum establish CV safety
- Evolution of regulatory guidance has dramatically altered the trial landscape of drug development for type 2 diabetes mellitus
  - >200,000 patients enrolled/planned in CV outcomes trials
  - 4 trials now reported demonstrating CV safety
  - EMPA REG outcome has reported CV efficacy with empagliflozin

Cardiometabolic Health Congress • March 4-5 • San Francisco, CA